ANALOGS OF DISCODERMOLIDE AND DICTYOSTATIN-1, INTERMEDIATES THEREFOR AND METHODS OF SYNTHESIS THEREOF

GOVERNMENT INTEREST

[0001] This invention was made with government support under grant CA 78039 awarded by the National Institutes of Health. The government has certain rights in this invention.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0002] The present application claims the benefit of U.S. Provisional Patent Application Serial No. 60/408,503, filed September 6, 2002 and U.S. Provisional Patent Application Serial No. 60/437,736 filed January 2, 2003, the disclosures of which are incorporated herein by reference.

BACKGROUND OF THE INVENTION

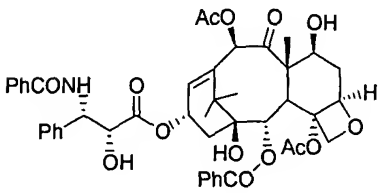
[0003] The present invention relates to analogs of discodermolide and dictyostatin-1, intermediates for the synthesis of such analogs and methods of synthesis of such intermediates and analogs.

[0004] References set forth herein may facilitate understanding of the present invention or the background of the present invention. Inclusion of a reference herein, however, is not intended to and does not constitute an admission that the reference is available as prior art with respect to the present invention.

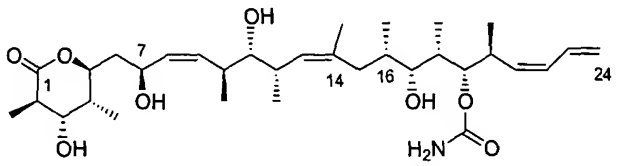
[0005] The discovery and development of new chemotherapeutic agents for the treatment of cancer is currently of high importance. Some of the best currently available chemotherapeutic agents are natural products or natural product analogs. For example, Taxol (paclitaxel) is a natural product that is currently being used to treat patients with breast and ovarian cancer among others. A number of analogs of Taxol, including Taxotere (docetaxel), are also powerful anticancer agents.

[0006] Recently, the natural product (+)-discodermolide and its analogs have shown great promise as anticancer agents. Discodermolide has been shown to have a mechanism of action similar to Taxol but it is active against Taxol-resistant cell lines and it is more water soluble than Taxol. Accordingly, it may have a different and/or broader spectrum of action than Taxol and be easier to formulate and administer. Like Taxol, discodermolide is difficult

to synthesize. Some syntheses of discodermolide are described in the following papers: Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. Total synthesis of the immunosuppressive agent (-)- discodermolide. *J. Am. Chem. Soc.* **1993**, *115*, 12621-12622; Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. Total Synthesis of (-)-Discodermolide. *J. Am. Chem. Soc.* **1995**, *117*, 12011-12012; Marshall, J. A.; Johns, B. A. Total synthesis of (+)-discodermolide. *J. Org. Chem.* **1998**, *63*, 7885-7892; Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. Total synthesis of the antimicrotubule agent (+)-discodermolide using boron-mediated aldol reactions of chiral ketones. *Angew. Chem., Int. Ed. Eng.* **2000**, *39*, 377-380; Paterson, I.; Florence, G. J. Synthesis of (+)-discodermolide and analogues by control of asymmetric induction in aldol reactions of gamma-chiral (Z)-enals. *Tetrahedron Lett.* **2000**, *41*, 6935-6939; Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y. P. et al. Evolution of a gram-scale synthesis of (+)-discodermolide. *J. Am. Chem. Soc.* **2000**, *122*, 8654-8664.



(–)-taxol

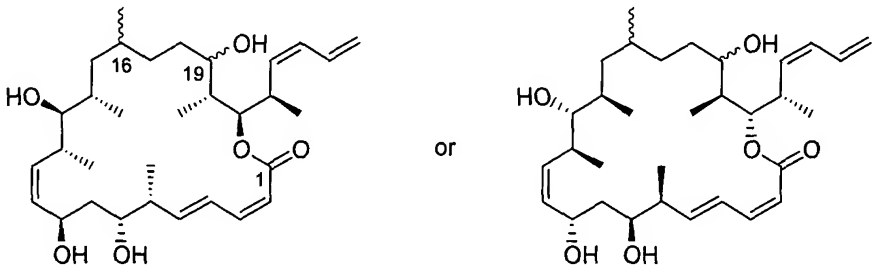


(+)-discodermolide

[0007] Analogs of discodermolide have also been made and tested for activity. For example, see the above references and Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. A practical synthesis of (+)-discodermolide and analogues: Fragment union by complex aldol reactions. *J. Am. Chem. Soc.* **2001**, *123*, 9535-9544; Martello, L. A.; LaMarche, M. J.; He, L.; Beauchamp, T. J.; Smith, A. B. et al. The relationship between taxol and (+)-discodermolide: synthetic analogs and modeling studies. *Chemistry Biol.* **2001**, *8*, 843-855; Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. Total Synthesis of (-)-Discodermolide: An Application of a Chelation-Controlled Alkylation Reaction. *J. Org. Chem.* **1997**, *62*, 6098-6099; Paterson, I.; Florence, G. J. Synthesis of (+)-discodermolide and analogues by control of asymmetric induction in aldol reactions of gamma-chiral (Z)-enals. *Tetrahedron Lett.* **2000**, *41*, 6935-6939.

[0008] Unlike Taxol, discodermolide is not readily available in large quantities from natural sources. Accordingly, assuring a sufficient supply of discodermolide is problematic. Simplified analogs that retain high anti-cancer activity but are easier to make are in urgent need.

[0009] Very recently, an unusual macrolactone natural product dictyostatin 1 has been isolated from two different sponges and a partial structure has been assigned as shown below. See Pettit, G. R.; Cichacz, Z. A. Isolation and structure of dictyostatin 1. In US 5,430,053; 1995; Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. Isolation and structure of the cancer cell growth inhibitor dictyostatin 1. *J. Chem. Soc., Chem. Commun.* **1994**, 1111-1112. The configurations at C16 and C19 have not yet been assigned in the natural product and the absolute configuration is not known. Dictyostatin shows extremely high potencies against and array of cancer cell lines.



dictyostatin 1
absolute configuration unknown, configurations at C16 and C19 unknown

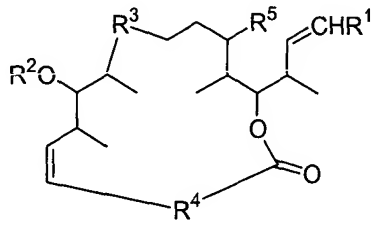
[0010] Recently, dictyostatin has also been shown to stabilize microtubules, like discodermolide and Taxol. See Wright, A. E.; Cummins, J. L.; Pomponi, S. A.; Longley, R. E.; Isbrucker, R. A. Dictyostatin compounds for stabilization of microtubules. In *PCT Int. Appl.*; WO62239, 2001. Accordingly, dictyostatin 1 and its analogs show great promise as new anticancer agents. There is an urgent need for a synthetic route to make dictyostatin 1 and its analogs in order to fully assign the structure of dictyostatin 1, to produce analogs to study the structure/activity relationship and to identify and produce the best possible drugs in this family.

[0011] The inventors of the present invention, as one aspect of the present invention, herein set forth a number of analogs of discodermolide, as well as methods and intermediates

for the synthesis thereof. The inventors of the present invention, as another aspect of the present invention, herein set forth a family of both closed and open analogs of dictyostatin 1 with methods and intermediates for the synthesis of this family.

SUMMARY OF THE INVENTION

[0012] In one aspect, the present invention provides a compound of the following structure:



wherein R^1 is H, an alkyl group, an aryl group, an alkenyl group, an alkynyl group, or a halogen atom;

R^2 is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

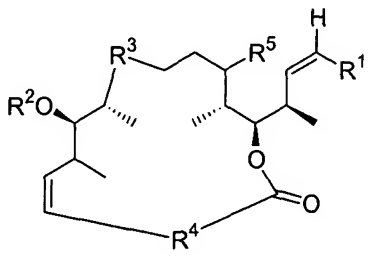
R^3 is $(CH_2)_n$ where n is and integer in the range of 0 to 5, $-CH_2CH(CH_3)-$, $-CH=CH-$, $-CH=C(CH_3)-$, or $-C\equiv C-$;

R^4 is $(CH_2)_p$ where p is an integer in the range of 4 to 12,
$-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})C(R^{s3})=C(R^{s4})-$,
$-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}CH(R^{s1})CH(R^{s2})C(R^{s3})=C(R^{s4})-$,
$-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})CH(R^{s3})CH(R^{s4})-$,
$-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}CH(R^{s1})CH(R^{s2})CH(R^{s3})CH(R^{s4})-$,
wherein y1 and y2 are 1 and y3, y4 and y5 are independently 0 or 1, R^{k1}, R^{k2}, R^{k3}, R^{k4} and R^{k5} are independently H, CH_3, or OR^{2a}, and R^{s1}, R^{s2}, R^{s3}, and R^{s4} are independently H or CH_3, wherein R^{2a} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e; and

R^5 is H or OR^{2b}, wherein R^{2b} is H, an alkyl group, an aryl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e; provided that the compound is not dictyostatin 1.

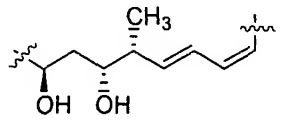
[0013] When groups including, but not limited to, $-SiR^aR^bR^c$, CH_2OR^d, and/or COR^e are set forth as a substituent for more than one group in compounds of the claims and the specification of the present invention (for example, as a substituent of R^2, R^{2a}, R^{s1}, R^{s2}, R^{s3}, R^{s4} and R^5 above), it is to be understood that the groups of those substituents (R^a, R^b, R^c,R^d, and R^e in this example), are independently, the same of different within each group and amoung the groups.

[0014] In one embodiment, the compound has the following stereostructure, or its enantiomer:

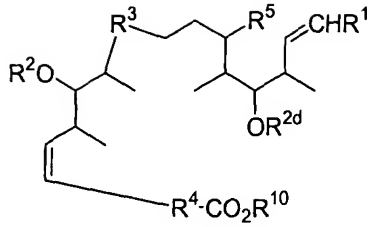


wherein R^1 is alkenyl; R^2 is H; R^3 is $-CH_2CH(CH_3)$ or $-CH=C(CH_3)$; and R^4 is $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})C(R^{s3})=C(R^{s4})-$ wherein y1-y4 are 1, y5 is 0, R^{k1} and R^{k3} are OH, R^{k2} is H, R^{k4} is CH_3, R^{s1}, R^{s2}, R^{s3} and R^{s4} are H, and R^5 is OH.

[0015] In one embodiment, R^1 is $-CH=CH_2$ and R^4 is



[0016] In another aspect, the present invention provides a compound of the following structure:



wherein R^1 is H, an alkyl group, an aryl group, an alkenyl group, an alkynyl group, or a halogen atom;

R^2 and R^{2d} are independently H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

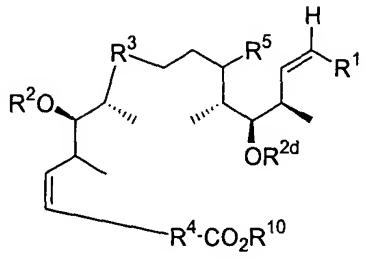
R^3 is $(CH_2)_n$ where n is and integer in the range of 0 to 5, $–CH_2CH(CH_3)–$, –CH=CH–, $-CH=C(CH_3)–$, or –C≡C–;

R^4 is $(CH_2)_p$ where p is an integer in the range of 4 to 12, $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})C(R^{s3})=C(R^{s4})-$, $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}CH(R^{s1})CH(R^{s2})C(R^{s3})=C(R^{s4})-$, $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})CH(R^{s3})CH(R^{s4})-$, $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}CH(R^{s1})CH(R^{s2})CH(R^{s3})CH(R^{s4})-$, wherein y1 and y2 are 1 and y3, y4 and y5 are independently 0 or 1, R^{k1}, R^{k2}, R^{k3}, R^{k4} and R^{k5} are independently H, $-CH_3$, or OR^{2a}, and R^{s1}, R^{s2}, R^{s3}, and R^{s4} are independently H or CH_3, wherein R^{2a} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e; and

R^5 is H or OR^{2b}, wherein R^{2b} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e; and

R^{10} is H or alkyl.

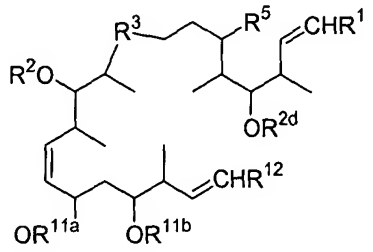
[0017] In one embodiment, the compound has the following stereostructure, or its enantiomer



wherein R^1 is alkenyl; R^2 is H; R^{2d} is H, $OC(O)CH_3$ or $OC(O)NR^gR^h$ wherein R^g and R^h are independently H, an alkyl group or an aryl group; R^3 is $CH_2CH(CH_3)$ or $CH=C(CH_3)$; and R^4 is $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})C(R^{s3})=C(R^{s4})-$ wherein y1-y4 are 1, y5 is 0, R^{k1} and R^{k3} are OH, R^{k2} is H, R^{k4} is CH_3, R^{s1}, R^{s2}, R^{s3} and R^{s4} are H, R^5 is OH; and R^{10} is H or alkyl.

[0018] In another embodiment, R^1 is $-CH=CH_2$, and R^{2d} is H, $OC(O)CH_3$ or $OC(O)NH_2$.]

[0019] In a further aspect, the present invention provides a compound of the following structure:



wherein R^1 is H, an alkyl group, an aryl group, an alkenyl group, an alkynyl group, or a halogen atom;

R^2 and R^{2d} are independently H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

R^3 is $(CH_2)_n$ where n is and integer in the range of 0 to 5, $-CH_2CH(CH_3)-$, $-CH=CH-$, $-CH=C(CH_3)-$, or $-C\equiv C-$;

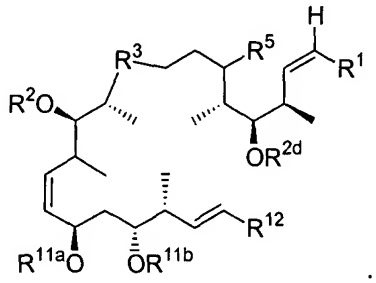
R^5 is H or OR^{2b}, wherein R^{2b} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^{11a} and R^{11b} are independently H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, COR^e, or R^{11a} and R^{11b} together form a portion of six-membered acetal ring incorporating CR^tR^u;

R^t and R^u are independently H, an alkyl group, an aryl group or an alkoxyarly group; and

R^{12} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10}, $CH=CHCH_2OR^{2c}$, CH=CHCHO, wherein R^{2c} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and R^{10} is H or alkyl.

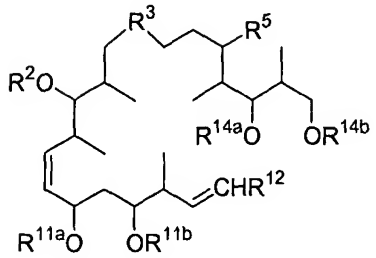
[0020] In one embodiment, the compound has the following stereostructure, or its enantiomer



wherein R^1 is alkenyl; R^{2d} is H, $OC(O)CH_3$ or $OC(O)NR^gR^h$ wherein R^g and R^h are independently H, an alkyl group or an aryl group; R^3 is $CH_2CH(CH_3)$ or $CH=C(CH_3)$; R^{11a} and R^{11b} are H or together form a portion of a six-membered acetal ring containing $C(H)(p\text{-}C_6H_4OCH_3)$ or $C(CH_3)_2$; R^{12} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10}, $CH=CHCH_2OR^{2c}$, CH=CHCHO, wherein R^{2c} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and R^{10} is H or alkyl.

[0021] In another embodiment, R^1 is $-CH=CH_2$, R^{2d} is H, $-OC(O)CH_3$ or $-OC(O)NH_2$, and R^{12} is $-CH_2OH$, -CHO or $-CO_2R^{10}$.

[0022] In another aspect, the present invention provides a compound having the following structure:



wherein R^2 is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

R^3 is $(CH_2)_n$ where n is and integer in the range of 0 to 5, $-CH_2CH(CH_3)-$, $-CH=CH-$, $-CH=C(CH_3)-$, or $-C\equiv C-$;

R^5 is H or OR^{2b}, wherein R^{2b} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

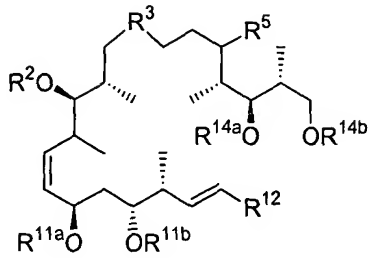
R^{11a} and R^{11b} are independently H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, COR^e, or R^{11a} and R^{11b} together form a portion of six-membered acetal ring containing CR^tR^u;

R^t and R^u are independently H, an alkyl group, an aryl group or an alkoxy aryl group;

R^{12} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10}, $CH=CHCH_2OR^{2c}$ or CH=CHCHO, $CH=CHCO_2R^{10}$, wherein R^{2c} is H, an alkyl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and R^{10} is H or alkyl; and

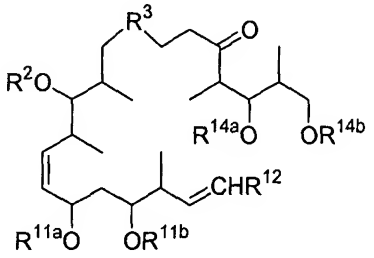
R^{14a} and R^{14b} are independently H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, COR^e, or R^{14a} and R^{14b} together form a six-membered ring containing CR^vR^w, wherein R^v and R^w are independently H, an alkyl group, an aryl group or an alkoxyaryl group.

[0023] In one embodiment, the compound has the following stereostructure, or its enantiomer



R^2 is H; R^{2d} is H, $OC(O)CH_3$ or $OC(O)NR^gR^h$ wherein R^g and R^h are independently H, an alkyl group or an aryl group; R^3 is $CH_2CH(CH_3)$ or $CH{=}C(CH_3)$; R^{11a} and R^{11b} are H or together form a portion of a six-membered acetal ring containing $C(H)(p\text{-}C_6H_4OCH_3)$ or $C(CH_3)_2$; R^{12} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10}, $CH{=}CHCH_2OR^{2c}$, CH=CHCHO or $CH{=}CHCO_2R^{10}$, wherein R^{2c} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and R^{10} is H or alkyl; and R^{14a} and R^{14b} are H or together form a portion of a six-membered acetal ring containing $C(H)(p\text{-}C_6H_4OCH_3)$ or $C(CH_3)_2$.

[0024] In another aspect, the present invention provides a compound having the following formula



wherein R^1 is H, an alkyl group, an aryl group, an alkenyl group, an alkynyl group, or a halogen atom;

R^2 is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

R^3 is $(CH_2)_n$ where n is and integer in the range of 0 to 5, $-CH_2CH(CH_3)-$, $-CH=CH-$, $-CH=C(CH_3)-$, or $-C\equiv C-$;

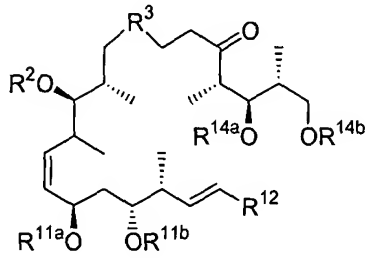
R^{11a} and R^{11b} are independently H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, COR^e, or R^{11a} and R^{11b} together form a portion of six-membered acetal ring containing CR^tR^u;

R^t and R^u are independently H, an alkyl group, an aryl group or an alkoxyarly group;

R^{12} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10}, $CH=CHCH_2OR^{2c}$, CH=CHCHO or $CH=CHCO_2R^{10}$, wherein R^{2c} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and R^{10} is H or alkyl; and

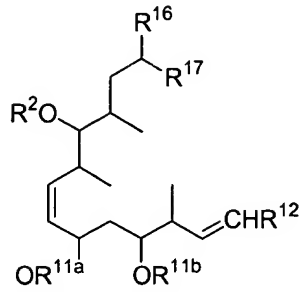
R^{14a} and R^{14b} are independently H, an alkyl group, and aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, COR^e, or R^{14a} and R^{14b} together form a six-membered ring containing CR^vR^w, wherein R^v and R^w are independently H, an alkyl group, an aryl group or an alkoxyaryl group.

[0025] In one embodiment, the compound has the following stereostructure, or its enantiomer



wherein R^3 is $CH_2CH(CH_3)$ or $CH=C(CH_3)$; R^{11a} and R^{11b} are H or together form a portion of a six-membered acetal ring containing $C(H)(p\text{-}C_6H_4OCH_3)$ or $C(CH_3)_2$; R^{12} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10}, $CH=CHCH_2OR^{2c}$, CH=CHCHO or $CH=CHCO_2R^{10}$, wherein R^{2c} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and R^{10} is H or alkyl; and R^{14a} and R^{14b} are H or together form a portion of a six-membered acetal ring containing $C(H)(p\text{-}C_6H_4OCH_3)$ or $C(CH_3)_2$.

In a further aspect, the present invention provides a compound having the following formula



wherein R^2 is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

R^{11a} and R^{11b} are independently H, an alkyl group, and aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, COR^e, or R^{11a} and R^{11b} together form a portion of six-membered acetal ring containing CR^tR^u;

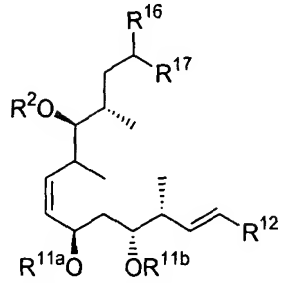
R^t and R^u are independently H, an alkyl group, an aryl group or an alkoxyarly group;

R^{12} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10}, $CH=CHCH_2OR^{2c}$, CH=CHCHO or $CH=CHCO_2R^{10}$, wherein R^{2c} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and R^{10} is H or alkyl;

R^{16} is H or alkyl; and

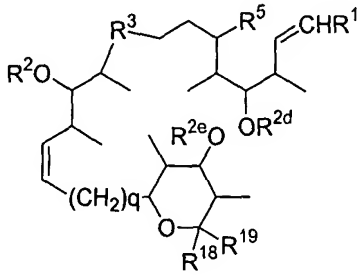
R^{17} is CH_2OR^{2f}, CHO, CO_2R^{10}, wherein R^{2f} is H, an alkyl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e.

[0026] In one embodiment, the compound has the following stereostructure, or its enantiomer



wherein R^2 is H, an alkyl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, R^{11a} and R^{11b} are H or together form a portion of a six-membered acetal ring containing $C(H)(p\text{-}C_6H_4OCH_3)$ or $C(CH_3)_2$; and R^{16} is H or alkyl.

[0027] In still a further aspect, the present invention provides a compound having the following formula



wherein R^1 is H, an alkyl group, an aryl group, an alkenyl group, an alkynyl group, or a halogen atom;

R^2, R^{2d} and R^{2e} are independently H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

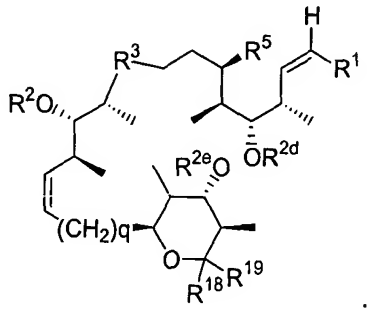
R^3 is $(CH_2)_n$ where n is and integer in the range of 0 to 5, $-CH_2CH(CH_3)-$, $-CH=CH-$, $-CH=C(CH_3)-$, or $-C\equiv C-$;

R^5 is H or OR^{2b}, wherein R^{2b} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

q is an integer in the range of 2 to 5;

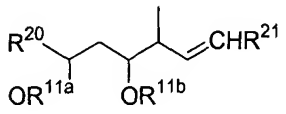
R^{18} is H, and R^{19} is hydroxy, alkoxy or $-SR^z$, wherein R^z is an alkyl group or an aryl group, or R^{18} and R^{19} taken together are =O.

[0028] In one embodiment, the compound has the following stereostructure, or its enantiomer



[0029] In one embodiment of the compound, R^1 is a $CH=CH_2$ and R^3 is (*Z*)-CH=CH–, or $-CH_2CH_2-$.

[0030] In a further aspect, the present invention provides a compound having the following structure



R^{11a} and R^{11b} are independently H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, COR^e, or R^{11a} and R^{11b} together form a portion of six-membered acetal ring containing CR^tR^u;

R^t and R^u are independently H, an alkyl group, an aryl group or an alkoxyarly group;

R^a, R^b and R^c are independently an alkyl group or an aryl group;

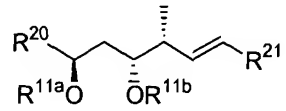
R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

R^{20} is CH_2OR^{2g}, CHO, CO_2R^{10}; wherein R^{2g} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and wherein R^{10} is H or alkyl; and

R^{21} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10a}, $CH=CHCH_2OR^{2c}$, CH=CHCHO or $CH=CHCO_2R^{10}$, wherein R^{2c} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and wherein R^{10a} is H or alkyl.

[0031] In one embodiment, the compound has the following stereostructure, or its enantiomer



wherein R^{11a} and R^{11b} are independently H, an alkyl group, and aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, COR^e, or R^{11a} and R^{11b} together form a portion of six-membered acetal ring incorporating CR^tR^u;

R^t and R^u are independently H, an alkyl, an aryl group or an alkoxyarly group;

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

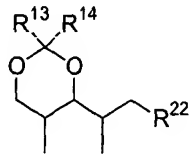
R^{20} is CH_2OR^{2g}, CHO, CO_2R^{10}; wherein R^{2g} is H, an alkyl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and wherein R^{10} is H or alkyl; and

R^{21} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10a}, $CH=CHCH_2OR^{2c}$, CH=CHCHO, $CH=CHCO^2R^{10}$ wherein R^{2c} is H, an alkyl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and wherein R^{10a} is H or alkyl.

[0032] In one embodiment, R^{11a} and R^{11b} are H or together form a portion of a six-membered acetal ring containing $C(H)(p\text{-}C_6H_4OCH_3)$ or $C(CH_3)_2$; R^{21} is a halogen atom, CH_2OR^{2c}, CHO, CO_2R^{10}, $CH{=}CHCH_2OR^{2c}$, CH=CHCHO, wherein R^{2c} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e, and R^{10} is H or alkyl.

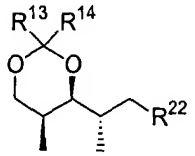
[0033] In another embodiment, R^1 is $CH{=}CH_2$, and R^{21} is CH_2OH, CHO or CO_2R^{10}.

[0034] In still another aspect, the present invention provides a compound having the following formula



wherein R^{13} is H or an alkyl group, R^{14} is H, an aryl group, an alkoxyaryl group or an alkyl group, and R^{22} is a halogen atom or $-P(Ar)_3X$, wherein X is a counteranion selected from the groups halide, tetrafluoroborate, hexafluorophosphate and sulfonate, provided that when R^{13} and R^{14} are methyl groups, X is not I. In one embodiment, when R^{13} and R^{14} are alkyl groups, X is not halogen.

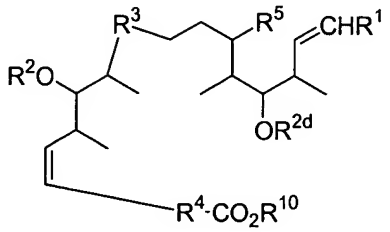
[0035] In another embodiment, the compound has the following stereostructure, or its enantiomer



wherein R^{13} is H or an alkyl group, and R^{14} is H, an aryl group, an alkoxyaryl group, or an alkyl group, an aryl group or an alkoxyarly group, R^{22} is a halogen atom or $-P(Ar)_3X$, wherein X is a counteranion selected from the groups halide, tetrafluoroborate, hexafluorophosphate and sulfonate, provided that when R^{13} and R^{14} are methyl groups, X is not I.

[0036] In one embodiment, R^{13} is H, R^{14} is aryl, and R^{22} is $P(C_6H_5)_3X$. In another embodiment, R^{14} is C_6H_4-*p*-OCH_3.

[0037] In still a further aspect, the present invention provides a process for conversion of a first compound with the formula



wherein R^1 is H, an alkyl group, an aryl group, an alkenyl group, an alkynyl group, or a halogen atom;

R^2 is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^{2d} is H

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

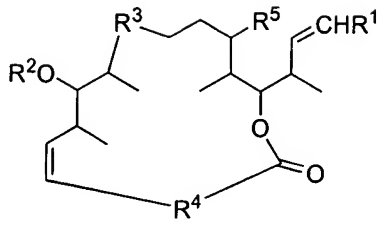
R^3 is $(CH_2)_n$ where n is and integer in the range of 0 to 5, $–CH_2CH(CH_3)–$, –CH=CH–, $-CH=C(CH_3)–$, or –C≡C–;

R^4 is $(CH_2)_p$ where p is an integer in the range of 4 to 12, $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})C(R^{s3})=C(R^{s4})-$, $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}CH(R^{s1})CH(R^{s2})C(R^{s3})=C(R^{s4})-$, $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})CH(R^{s3})CH(R^{s4})-$, $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}CH(R^{s1})CH(R^{s2})CH(R^{s3})CH(R^{s4})-$, wherein y1 and y2 are 1 and y3, y4 and y5 are independently 0 or 1, R^{k1}, R^{k2}, R^{k3}, R^{k4} and R^{k5} are independently H, CH_3, or OR^{2a}, and R^{s1}, R^{s2}, R^{s3}, and R^{s4} are independently H or CH_3, wherein R^{2a} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e; and

R^5 is H or OR^{2b}, wherein R^{2b} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e; and

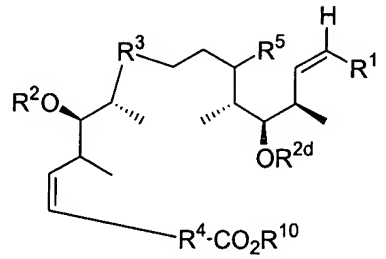
R^{10} is H;

to a second compound with the formula



comprising the step of reacting the first compound under conditions suitable to effect macrolactonization.

[0038] In one embodiment, the process is for conversion of a compound with the following stereostructure or its enantiomer



wherein R^1 is H, an alkyl group, an alkenyl group, an alkynyl group, or a halogen atom;

R^2 is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^{2d} is H

R^a, R^b and R^c are independently an alkyl group or an aryl group;

R^d is an alkyl group, an aryl group, an alkoxylalkyl group, $-R^iSiR^aR^bR^c$ or a benzyl group, wherein R^i is an alkylene group;

R^e is an alkyl group, an allyl group, a benzyl group, an aryl group, an alkoxy group, or $-NR^gR^h$, wherein R^g and R^h are independently H, an alkyl group or an aryl group;

R^3 is $(CH_2)_n$ where n is and integer in the range of 0 to 5, $-CH_2CH(CH_3)-$, $-CH=CH-$, $-CH=C(CH_3)-$, or $-C\equiv C-$;

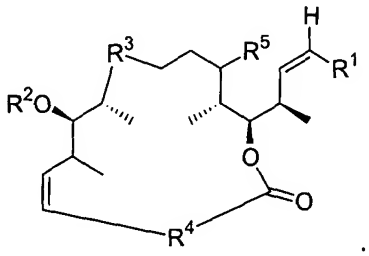
R^4 is $(CH_2)_p$ where p is an integer in the range of 4 to 12, $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})C(R^{s3})=C(R^{s4})-$,

$-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}CH(R^{s1})CH(R^{s2})C(R^{s3})=C(R^{s4})-$,
$-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})CH(R^{s3})CH(R^{s4})-$,
$-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}CH(R^{s1})CH(R^{s2})CH(R^{s3})CH(R^{s4})-$,
wherein y1 and y2 are 1 and y3, y4 and y5 are independently 0 or 1, R^{k1}, R^{k2}, R^{k3}, R^{k4} and R^{k5} are independently H, $-CH_3$, or OR^{2a}, and R^{s1}, R^{s2}, R^{s3}, and R^{s4} are independently H or CH_3, wherein R^{2a} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e;

R^5 is H or OR^{2b}, wherein R^{2b} is H, an alkyl group, an aryl group, a benzyl group, a trityl group, $-SiR^aR^bR^c$, CH_2OR^d, or COR^e; and

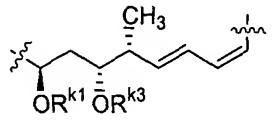
R^{10} is H

to a second compound with the formula



[0039] In one embodiment of the process, R^1 is alkenyl; R^3 is $CH_2CH(CH_3)$ or $CH=C(CH_3)$; and R^4 is $-(CHR^{k1})_{y1}(CHR^{k2})_{y2}(CHR^{k3})_{y3}(CHR^{k4})_{y4}(CHR^{k5})_{y5}C(R^{s1})=C(R^{s2})C(R^{s3})=C(R^{s4})-$ wherein y1-y4 are 1, y5 is 0, R^{k1} and R^{k3} are R^{2a}, R^{k2} is H, R^{k4} is CH_3, R^{s1}-R^{s4} are H, and R^5 is OR^{2b}.

[0040] In another embodiment of the process, R^1 is $CH=CH_2$ and R^4 is



[0041] In one embodiment of the process, the first compound is converted by reacting the first compound with 2,4,6-trichlorobenzoylchloride.

[0042] The above general structures for the compounds of the present invention include all stereoisomers thereof (other than the natural compound dictyostatin 1). Moreover,

the structures of the compounds of the present invention include the compounds in racemic form, enantiomerically enriched form or enantiomerically pure form.

[0043] The terms "alkyl", "aryl" and other groups refer generally to both unsubstituted and substituted groups unless specified to the contrary. In that regard, the groups set forth above can be substituted with a wide variety of substituents to synthesize analogs retaining biological activity. Unless otherwise specified, alkyl groups are hydrocarbon groups and are preferably C_1-C_{15} (that is, having 1 to 15 carbon atoms) alkyl groups, and more preferably C_1-C_{10} alkyl groups, and can be branched or unbranched, acyclic or cyclic. The above definition of an alkyl group and other definitions apply also when the group is a substituent on another group (for example, an alkyl group as a substituent of an alkylamino group or a dialkylamino group). The term "aryl" refers to phenyl or naphthyl. As used herein, the terms "halogen" or "halo" refer to fluoro, chloro, bromo and iodo.

[0044] The term "alkoxy" refers to -OR, wherein R is an alkyl group. The term "alkenyl" refers to a straight or branched chain hydrocarbon group with at least one double bond, preferably with 2-15 carbon atoms, and more preferably with 2-10 carbon atoms (for example, -CH=CHR or -CH_2CH=CHR; wherein R can be a group including, but not limited to, an alkyl group, an alkoxyalkyl group, an amino alkyl group, an aryl group, or a benzyl group). The term "alkynyl" refers to a straight or branched chain hydrocarbon group with at least one triple bond, preferably with 2-15 carbon atoms, and more preferably with 2-10 carbon atoms (for example, -C≡CR or –CH_2-C≡CR; wherein R can be a group including, but not limited to, an alkyl group, an alkoxyalkyl group, an amino alkyl group, an aryl group, or a benzyl group). The terms "alkylene," "alkenylene" and "alkynylene" refer to bivalent forms of alkyl, alkenyl and alkynyl groups, respectively.

[0045] The term "trityl" refers to a triphenyl methyl group or -$C(Ph)_3$.

[0046] Certain groups such as amino and hydroxy groups may include protective groups as known in the art. Preferred protective groups for amino groups include *tert*-butyloxycarbonyl, formyl, acetyl, benzyl, *p*-methoxybenzyloxycarbonyl, trityl. Other suitable protecting groups as known to those skilled in the art are disclosed in Greene, T., Wuts, P.G.M., *Protective Groups in Organic Synthesis*, Wiley (1991), the disclosure of which is incorporated herein by reference.

[0047] Other aspects of the present invention include the synthesis of the compounds of the preent invention as well as the biological assaying of such compound and the

biological activity of such compounds against, for example, cancer (such as breast, prostate cancer and ovarial cancer). For example, in another aspect, the present invention provides a method of treating a patient for cancer, including the step of administering a pharmaceutically effective amount of a biologically active compound of the present invention or a pharmaceutically acceptable salt thereof.

[0048] The present invention, along with the attributes and attendant advantages thereof, will best be appreciated and understood in view of the following detailed description taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0049] Figure 1 illustrates one embodiment of the syntheses of a representative isomeric aldehyde for incorporation of the left part of the configuration of (+)-discodermolide.

[0050] Figure 2 illustrates one embodiment of the syntheses of another representative isomeric aldehyde for incorporation of the left part of the configuration of (+)-discodermolide.

[0051] Figure 2 illustrates one embodiment of the syntheses of an intermediate for the center part of the configuration of (+)-discodermolide.

[0052] Figure 4 illustrates one embodiment of the construction of the right fragment or part of the molecule.

[0053] Figure 5 illustrates an embodiment of the synthesis of several discodermolide analogs of the present invention.

[0054] Figures 6A through D illustrate the tubulin polymerization-inducing properties of discodermolide (Figure A), as well as discodermolide analog compounds **40** (Figure B), **41** (Figure C) and **42** (Figure D) of the present invention in comparison to 10 μM paclitaxel (PTX).

[0055] Figure 7 illustrates a retrosynthetic analysis of a dictyostatin analog of the present invention.

[0056] Figure 8 illustrates an embodiment of the coupling of three fragments of a dictyostatin analog of the present invention.

[0057] Figure 9 illustrates the structures of several acyclic compounds of the present invention that were tested for biological activity.

[0058] Figure 10 illustrates an embodiment of the synthesis of a lower fragment of a dictyostatin analog of the present invention.

[0059] Figure 11 illustrates an embodiment of the synthesis of a macrolactone of the present invention.

[0060] Figure 12 illustrates a second representative general scheme for synthesis of stereoisomers and analogs of dictyostatin.

[0061] Figure 13 illustrates a summary of an embodiment of the synthesis of the bottom fragment of dictyostatin analogs of the present invention.

[0062] Figure 14 illustrates an embodiment of the coupling of the bottom fragment of Figure 13 with the center fragment of the dictyostatin analogs of the present invention.

[0063] Figure 15 illustrates an embodiment of the introduction of the C16 stereocenter and introduction of the top fragment of the dictyostatin analog of the present invention.

[0064] Figure 16 illustrates an embodiment of the completion of the synthesis of the dictyostatin analog of the present invention.

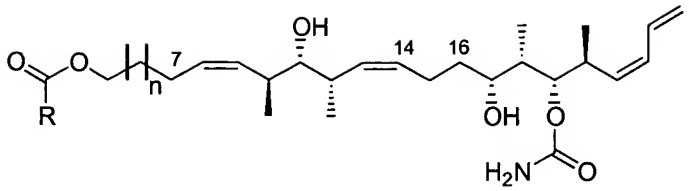
[0065] Figure 17 illustrates embodiments of representative methods to make analogs of the terminal diene fragment of the dictyostatin analog of the present invention.

[0066] Figure 18 illustrates a summary of an embodiment of the synthesis of the bottom fragment of the dictyostatin analog of the present invention.

[0067] Figure 19 illustrates an embodiment of the synthesis of two fragments with anti/anti configurations as assigned to dictyostatin 1 at C13-C15.

DETAILED DESCRIPTION OF THE INVENTION

[0068] **Synthesis of Simplified Analogs of Discodermolide:** The inventors of the present invention hypothesized that active analogs of discodermolide would result after removal of the C14 and C16 methyl groups and the C7 hydroxy group. These deletions greatly simplify the synthesis by allowing the two cis-disubstituted alkenes of analogs **1** and **2** to be made by Wittig-type reactions. A family of simple analogs **1** were shown to have moderate activity. However, by incorporating a lactone in place of the simple ester side chains of **1**, the inventors of the present invention have discovered anti-cancer agents of increased activity that are still significantly simpler to make than discodermolide.



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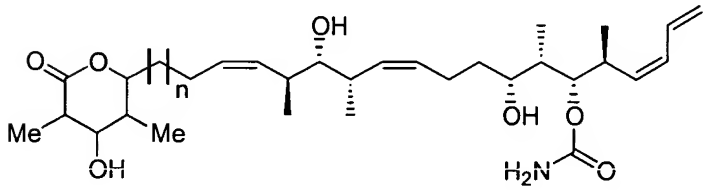

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[0069] The syntheses of two representative isomeric aldehydes **9a** and **9b** for incorporation of the left part of these molecules are shown in Figures 1 and 2. he synthesis of the left display bearing the configuration of (+)-discodermolide started with the commercially available methacrolein **3** (Figure 1). Reaction of **3** with the boron enolate of Evans oxazolidinone **4** gave the corresponding alcohol, which was silylated to give compound **5** in 90% yield. Lactonization followed by the introduction of allyl group was performed by the previously reported method to give **6** in good yield. See Day, B. W.; Kangani, C. O.; Avor, K. S. Convenient syntheses of (2R,3S,4R)-3-(tert-butyldimethylsilanyloxy)-2,4-dimethyl-5-oxopentanoic acid methoxymethyl-amide from methacrolein. Preparation of C1-C7 and C17-C24 fragments of (+)-discodermolide. *Tetrahedron Asymmetry* **2002**, *13*, 1161-1165. Lactone opening, oxidation and allylation gave **7**. Conversion to the methyl acetal was accomplished by DIBAL (diisobutylaluminum hydride) reduction to the corresponding lactol followed by treatment with camphorsulfonic acid (CSA) in methanol to give a desilylated intermediate, which was protected with methoxymethyl chloride (MOMCl) to give a mixture of anomers **8** (β:α = 1:1). These were separable by silica gel flash chromatography. The final left fragment **9a** was obtained by hydroboration of the α-anomer **8** with BH_3-DMS (borane-dimethysulfide) followed by oxidation with SO_3-pyridine.

[0070] The synthesis of the C4-epi lactone left display **9b** started from 1,4-butanediol (Figure 2). Monoprotection with PMB bromide (PMB is *p*-methoxybenzyl) was performed with NaH in DMF. After oxidation, reaction of the crude aldehyde **10** with the boron enolate

of Evans oxazolidinone **4** gave the corresponding *syn*-alcohol, which was silylated to give compound **11** in 90% yield. Lithium borohydride reduction followed by oxidation gave the aldehyde **12**. A second *syn*-aldol addition was performed with same Evans oxazolidinone **4** to give the corresponding alcohol, which was protected with MOM chloride to give compound **13**. Desilylation of **13** with HF gave the cyclized product **14** in high yield. Conversion to the methyl acetal was easily accomplished by DIBAL reduction to the corresponding lactol followed by treatment with PPTS (pyridinium *p*-toluene sulfonate) in methanol to give **15** as a 2.5:1 (α:β) mixture of anomers from which the major anomer (α) was isolated by silica gel flash chromatography. The final left fragment **9b** was obtained by hydrogenolysis of the PMB protecting group followed by Dess-Martin oxidation.

[0071] These synthetic routes are flexible and substantially any stereoisomer of the lactone **9** can be made with the appropriate chiral auxiliary and reaction conditions.

[0072] Center intermediate **21** was prepared as shown in Figure 3. Oxazolidinone **18** was prepared from (*S*)-3-hydroxy-2-methylpropionic methyl ester **16** by the known procedure for the preparation of *ent*-**18**. See Clark, D. L.; Heathcock, C. H. Studies on the alkylation of chiral enolates: application toward the total synthesis of discodermolide. *J. Org. Chem.* **1993**, *58* 5878–5879. Reduction of **18** with lithium borohydride gave the diol, which was protected by anisaldehyde dimethyl acetal **19** to give the acetal **20**. Deprotection of the primary TBS group with tetrabutylammonium fluoride (TBAF), iodination, and treatment with triphenylphosphine afforded the phosphonium salt **21** in 72% yield. Phosphonium salts **22** and **23** were also used for Wittig olefination, but the results were unsatisfactory. Smith also encountered difficulties with related Wittig reagents in discodermolide synthesis. See: Smith, A. B.; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y. P. et al. Evolution of a gram-scale synthesis of (+)-discodermolide. *J. Am. Chem. Soc.* **2000**, *122*, 8654-8664. These difficulties may result, at least in part, from the hygroscopic nature of the phosphonium salts. In contrast, compound **21** is a white, non-hygroscopic solid and its Wittig reactions were reliable even though no special care was taken with its storage (for example, salt **21** was useful for reactions even after it was stored at room temperature for several months).

[0073] As shown in Figure 4, the construction of the right fragment **34** featured aldol reactions. *Syn*-Aldol reaction of aldehyde **24** with **4** provided **25**, which was reduced to a diol and protected with anisaldehyde dimethyl acetal **19** to give **26**. Selective opening of the benzylidine ring of **26** with DIBAL gave a primary alcohol, which was oxidized to aldehyde **27**. The subsequent *anti*-aldol condensation using Heathcock's aldol reaction with

dimethylphenyl propionate **28** furnished compound **29** as the major product in 73% yield. See Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. Acyclic stereoselection-13; Aryl esters: reagents for threo-aldolization. *Tetrahedron* **1981**, *37*, 4087–4095. The relative configuration of intermediate **29** was confirmed by ^{13}C and ^{1}H NMR analyses of the corresponding acetonide **34**. Silylation of the newly formed hydroxyl group of **29**, reduction of the aryl ester with DIBAL and Dess-Martin oxidation of the resultant primary alcohol afforded aldehyde **30**. The *Z*-diene moiety was introduced by a two-step procedure developed by Paterson and coworkers using a Nozaki-Hiyama reaction. See Paterson, I.; Schlapbach, A. Studies towards the total synthesis of the marine-derived immunosuppresant discodermolide: stereoselective synthesis of a C9-C24 subunit. *Synlett.* **1995**, 498–500. Addition of the aldehyde **30** and allyl bromide **31** to a suspension of $CrCl_2$ in THF produced an intermediate β-hydroxy silane (not shown), which upon treatment with NaH underwent *syn* elimination to generate the required *Z*-diene **32**. Selective deprotection of the primary TBS group, iodination, and then treatment with triphenylphosphine gave the phosphonium salt **33** in good yield.

[0074] The first Wittig reaction of **9a** with **21** provided **35** (see Figure 5). DIBAL reductive cleavage of the acetal followed by Dess-Martin oxidation gave aldehyde **37**. Likewise, aldehyde **38** was made from **9b** via **36**. The second Wittig olefination was accomplished with **38** as an example and phosphonium salt **33** (Figure 5). Tetrabutylammonium fluoride deprotection followed by carbamoylation using Koçovsky's method (See Koçovsky, P. Carbamates: a method of synthesis and some synthetic applications. *Tetrahedron Lett.* **1986**, *27* 5521–5524) afforded the C19 carbamate-containing compound **39**. The lactone was built from the methyl acetal in the left fragment by using aqueous 60% acetic acid in THF followed by Dess-Martin oxidation. Deprotected analog **40** containing a free C3 hydroxy group on the lactone was obtained by the removal of MOM group with 4N HCl followed by removal of the PMB protecting groups with DDQ oxidation. Two additional example compounds, **41** and **42**, were prepared from the intermediate **39** by using appropriate conditions. All three of these analogs exhibited significant activity, as shown in Figures 6A-D and Table 1. Surprisingly, the C3-MOM-protected analogs **41** and **42** showed better microtubule hypernucleation activities than the analog **40** with a free C3-hydroxy group. As can be seen in Figure 6A, discodermolide is superior to paclitaxel (taxol) in that it causes equivalent microtubule assembly at both lower concentrations and temperatures (the increase in absorbance caused by discodermolide occurs at a time point

earlier than that caused by paclitaxel). Additionally, the polymer induced to form by discodermolide is more resistant to cold-induced disassembly than is the paclitaxel-induced polymer. Both analogs **41** (Figure 6C) and **42** (Figure 6D) showed these more rapid polymer-inducing and cold-resistant properties, albeit at somewhat lower potencies (for example, higher concentrations of the analogs were necessary for these effects to be detected) than discodermolide. MOM ether lactone **41** was the most potent among these analogs.

[0075] Table 1 shows microtubule stabilizing, antiproliferative, and paclitaxel-displacing properties of **40-42**. Again, the lactone, MOM ether **41** was more potent than the lactol **42** or free hydroxy **40** relatives. The cellular activity of **41** was good, showing a submicromolar 50% growth inhibitory (GI_{50}) concentration. This compound also showed considerable affinity for the paclitaxel binding site on tubulin. A 2-fold molar excess of **41** displaced [^{3}H]paclitaxel from microtubules better than paclitaxel and at almost the same potency as discodermolide.

Table 1. Microtubule stabilizing, antiproliferative and paclitaxel-displacing properties of compounds **40-42** in comparison to (+)-discodermolide (**1**) and paclitaxel.

Compound	MT stabilizing activity (%)[a]	GI_{50} (μM)[b]			Displacement of [^{3}H]paclitaxel (%)[c]
		MDA-MB231 (breast)	PC3 (prostate)	2008 (ovarian)	
discodermolide	>100	0.016±0.003	0.067±0.004	0.072±0.005	64±2
paclitaxel	100	0.0024±0.0016	0.015±0.002	0.0092±0.0016	37±1
40	11	2.1±1.8	7.5±2.0	5.2±1.0	21±1
41	27	0.87±0.21	1.8±0.9	0.65±0.25	57±2
42	11	3.4±0.8	15±3	4.7±0.6	19±2

[a]Percent tubulin assembly induced by test agent at 10 μM vs. that caused by 10 μM paclitaxel (100%); single determinations at 30 °C. [b]Concentration at which test agent caused 50% inhibition of cell growth; means (N = 4 over 10 concentrations) ± SD after 72 h of continuous exposure to the agent. [c]Percent displacement by 4 μM test agent of 2 μM [^{3}H]paclitaxel bound to microtubules formed from 2 μM tubulin and 20 μM dideoxyGTP.

[0076] Macrocycle **43** is a representative example of a dictyostatin analog with an alkyl chain bridging the lactone carbonyl group and the C10/C11 alkene and with two Z-double bonds in the macrocycle. It can also be considered as a macrocyclic analog of discodermolide. This can be synthesized convergently from three components—**33**, **21** and **44**—via sequential Wittig couplings and a macrocyclization (Figure 7). This design allows

the synthesis of substantially any stereoisomer by employing the desired isomer of the relevant precursor—**21** or **33**.

[0077] Fragment **45** was synthesized from 1,10-decanediol (not shown) by mono-TBS protection (NaH/TBSCl, 42%) followed by Dess-Martin oxidation (80%). Fragment **21** was prepared as shown in Figure 3. Fragment **33** was prepared as shown in Figure 4.

[0078] The coupling of the three fragments is summarized in Figure 8. Generation of the ylide from phosphonium salt **21** and NaHDMS followed by addition of aldehyde **44** gave the Wittig product in good yield (75%) provided that the reaction was conducted at high concentration (1M in **21**). The formation of the *Z*-alkene was confirmed by the 10 Hz coupling constant between the vinyl protons. Selective opening of the PMB acetal was accomplished by addition of 3 equiv of DIBAL to give a primary alcohol. This was oxidized to an aldehyde under Dess-Martin conditions. Wittig conditions similar to those above were then deployed to prepare **45** from this aldehyde and phosphonium salt **33**.

[0079] Selective deprotection of **45** was achieved using HF-pyridine and the resulting primary alcohol was oxidized to acid **46**. The other TBS group was then removed with TBAF. Using the Yamaguchi protocol, the macrolactone ring was then constructed. PMB deprotection using DDQ provided target product **43**, whose protons and carbons were assigned by COSY and HMQC NMR experiments. The location of the macrolactone ring was confirmed by HMBC NMR experiments.

[0080] Acyclic compounds **47**, **48** and **49** were readily made from appropriate synthetic intermediates (**45** or **46**) in reasonable yields (Figure 9).

[0081] These analogs were tested for antiproliferative activity *in vitro* against two human cancer cell lines (Table 2). Macrolactone **43** and non-cyclized alcohol **47** and ester **48** exhibited similar 50% growth inhibitory concentrations, in the 15-30 μM range. Carboxylic acid **49** was inactive (>50 μM) possibly due to poor cell membrane penetration. The modest activity of these compounds is encouraging given the simplicity and flexibility of their lower chain.

[0082] We therefore decided to introduce the more complex bottom part of dictyostatin-1 lacking only the C9'–OH group. The synthesis of a lower fragment more closely related to dictyostatin is shown in Figure 10. Synthesis of the needed aldehyde **51** (Figure 10) started from the intermediate **25**, which was reduced to an alcohol with $LiBH_4$, followed by PMB acetal protection as in Figure 4. Selective acetal opening produced alcohol **50**, which was subjected to Dess-Martin oxidation to give aldehyde **27** (see Figure 4).

Wittig-Horner reaction, and removal of the TBS group with HF-pyridine gave a primary alcohol, which was oxidized to aldehyde **51**.

[0083] Center part Wittig salt **21** (Figure 3) was reacted with aldehyde **51** to give the (*Z*)-olefin (Figure 11). This was followed by selective PMP acetal opening with $NaCNBH_3$-TMSCl to yield a primary alcohol. The aldehyde obtained after Dess-Martin oxidation was again subjected to Wittig reaction with **33** to generate **52**. Ester **52** was reduced to the alcohol with DIBAL, followed by Dess-Martin oxidation and application of the Still (*Z*)-variant of the Wittig reaction to afford (*E,Z*) doubly unsaturated ester **53**. Selective removal of the TBS groups was accomplished by exposure to 3N HCl-MeOH in THF (1:1). The resulting ester was hydrolyzed by using 1N KOH in refluxing in EtOH. Finally, the Yamaguchi lactonization protocol followed by DDQ deprotection gave macrolactone **54**, whose structure was confirmed by HMBC and other NMR experiments. No isomerization of either of the dienes or the isolated *cis*-alkenes was detected.

[0084] Compound **54** proved to be quite potent in terms of antiproliferative activity against human carcinoma cells (Table 2) showing a 50% growth inhibitory concentration against breast and ovarian cancer cells of about 1 μM. Furthermore compound **54** displaced [^{3}H]paclitaxel stoichiometrically bound to microtubules at about 1/3rd the potency of discodermolide.

Table 2. Human Cancer Cell Growth Inhibitory and Paclitaxel Displacing Properties of Macrolactone Discodermolide Analogs

	GI_{50}(μM)[a]		Displacement of [^{3}H]paclitaxel (%)[c]
	MDA-MB-231 (breast)	2008 (ovary)	
43	27 ± 1	16 ± 1	18 ± 5
47	18 ± 1	22 ± 5	21 ± 2
48	26 ± 3	19 ± 2	17 ± 1
49	> 50	> 50	16 ± 3
54	1.4 ± 0.1[b]	1.0 ± 0.1[b]	27 ± 8
discodermolide	0.016 ± 0.003[b]	0.072 ± 0.005[b]	64 ± 2

[a]Fifty percent growth inhibitory concentration after 48 or 72[b] hours of continuous exposure (mean ± standard deviation; N = 4).
[c]Percent displacement by 4 μM test agent of 2 μM [^{3}H]paclitaxel bound to microtubules formed from 2 μM tubulin and 20 μM dideoxyGTP (N = 6, means ± SD).

[0085] A second representative general strategy for the synthesis of stereoisomers and close analogs of dictyostatin is shown in Figure 12. Again the molecule is dissected such that

every stereocenter can be controlled and modified either by starting with an appropriate precursor or through an asymmetric reaction allowing access to both possible isomers.

[0086] Figure 13 summarizes the synthesis of the bottom fragment. (S)-Diethyl maleate was reduced and the resulting diol was converted to acetonide **55**. Reduction to the aldehyde and standard Evans aldol reaction gave **56**. Reduction of this to the aldehyde and Wittig-Horner Emmons reaction gave **57**. Removal of the acetonide and silyation gave **58**, which was mono-desilylated to **59** and oxidized to aldehyde **60**.

[0087] Coupling of the bottom fragment with the center fragment and elaboration are shown in Figure 14. Wittig reaction of **21** (Figure 3) and **60** proceeded smoothly to form **61**, which was hydrolyzed and reduced to give **62**. After tritylation to **63**, DIBAL reduction gave **64**. Oxidation and Wittig-Horner reaction produced **65**, which was reduced to give **66** and hydrolyzed to acid **67**. Activation of **67** as the mixed anhydride preceded conversion to the oxazolidinone **68**.

[0088] Introduction of the C16 stereocenter and introduction of the top fragment are shown in Figure 15. Evans asymmetric alkylation to **69** followed by removal of the chiral auxiliary by reduction gave **70**. Separately, reagent **71** was made from the Evans oxazolindinone by displacement with $LiCH_2P(O)(OMe)_2$. Dess-Martin oxidation and Horner-Emmons olefination with **71** then gave **72**, which was reduced with $NiCl_2/NaBH_4$ to **73**. Now reduction with sodium borohydride gave a 2.8/1 mixture of stereoisomers, which could be separated and converted to the final products independently. Silylation to **75** followed by DIBAL reduction gave **76**, which was converted to diene **77** as described above. Detriylation then gave **78**.

[0089] Completion of the synthesis is shown in Figure 16. Dess-Martin oxidation and Still-Gennari olefination gave **79** which was deprotected with DDQ to **80**. Saponification then gave the hydroxy acid **81** ready for macrocyclization. Treatment of **81** under the Yamaguchi protocol gave **82**, which was finally deprotected to give the target product **83**, an isomer of dictyostatin 1 called dictyostatin 5.

[0090] Representative methods to make analogs of the terminal diene fragment are shown in Figure 17. Alkene **84** was ozonized to give the aldehyde, which was subjected to a Wittig reaction to give analogs like **85**. Alternatively, **84** can be converted to the Z-vinyl iodide **86**, which can in turn be coupled with organometallic reagents like phenyl zinc iodide to give **87**. This combination of olefination and organometallic and related coupling methods allows access to a wide variety of groups in this position.

[0091] The versatility of the synthesis is illustrated by the preparations of representative additional fragments that can be used to make dictyostatin, its isomers and its analogs. Figure 18 summarizes the synthesis of a fully elaborated bottom fragment **92**. Acetal **88**, readily prepared from (D)-malic acid, was silylated with t-butyldiphenylsilyl chloride (TBDPSCl). Reductive cleavage of the acetal with DIBAL followed by Swern oxidation provided aldehyde **89**. Reaction of **89** with the indicated Z-crotyl boronate according to Roush (See: Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. Asymmetric synthesis using tartrate modified allyl boronates. 2. Single and double asymmetric reactions with alkoxy-substituted aldehydes, *J. Org. Chem.* **1990**, *55*, 4117-4126) provided **90** in 63% isolated yield. PMB protection, ozonolysis and Wittig-Horner olefination then gave **91**. This was converted to the E/Z diene **92** by DIBAL reduction, Dess-Martin oxidation, Still-Gennari olefination and desilylation with HF/pyridine.

[0092] Figure 19 shows the synthesis of two fragments with anti/anti configurations as assigned to dictyostatin 1 at C13-C15. Evan *anti*-aldol reaction of ent-**4** and methacrolein (See: Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. Diastereoselective magnesium halide-catalyzed *anti*-aldol reactions of chiral N-acyloxazolidinones. *J. Am. Chem. Soc.* **2002**, *124*, 392-393) followed by TFA treatment gave **93** in 78% yield. A minor diastereomer of **93** (about 16/1 ratio) was separated by chromatography. Silylation of **93** followed by hydroboration and oxidation provided alcohol **94** in 75% yield alongside the lactone resulting from cyclization of the terminal hydroxyl group with displacement of the chiral auxiliary (not shown, 10% yield). Silylation of **94** and reductive cleavage of the auxiliary provided **95**, which was oxidized to **96** by the Swern method. Related aldehyde **98** was made by Roush allylboration of ent-**17** (see **17** in Figure 3) with the indicated E-crotylborate (mismatched case, 4/1 selectivity) to give **97**, followed by reaction with PMBBr and ozonolysis.

Examples

[0093] **(4*R*)-4-Benzyl-3-[(2*R*,3*R*)-3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethylpent-4-enoyl]oxazolidin-2-one (5).** TBDMSOTf (3.44 mL, 15 mmol) was added to a stirred solution of aldol product (3.03 g, 10 mmol) and 1,6-lutidine (2.32 mL, 20 mmol) in CH_2Cl_2 (20 mL) at –78 °C and the mixture was stirred for 2 h at ambient temperature. The reaction was quenched by the addition of aqueous HCl (0.5 N, 50 mL). The resulting mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$ followed by the evaporation of solvent

under reduced pressure. The product was purified by short column chromatography (hexane/EtOAc 9:1). Crude **5** was used without purification.

[0094] **(2*S*,3*R*,4*S*,5*R*)-2-Allyl-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran (8).** Diisobutylaluminum hydride (1.0 M in THF, 3.3 mL, 3.3 mmol) was added dropwise to a stirred solution of **7** (894 mg, 3 mmol) in anhydrous CH_2Cl_2 (30 mL) under an atmosphere of N_2 at –78 °C and the resulting mixture was stirred for an additional 1 h at –78 °C. The reaction was quenched by the careful addition of saturated aqueous potassium sodium tartrate (50 mL) and stirred for 3 h at room temperature. Once the organic and aqueous layers had separated, the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The crude lactol was used for the next reaction without further purification.

[0095] A solution of the lactol and CSA (0.3 mmol) in MeOH was stirred for 24 h at room temperature. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was used for the next reaction.

[0096] *N,N*-Diisopropylethylamine (7.5 mL) and chloromethyl methyl ether (1.13 mL, 15 mmol) were added to a solution of the alcohol in CH_2Cl_2 (15 mL). The reaction mixture was heated to reflux and stirred overnight. The reaction was quenched with aqueous saturated $NaHCO_3$ (50 mL) followed by washing with brine. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/EtOAc 7:3) to provide the pure anomers of **8** (β, 33 %; α, 32 %). $\tilde{\beta}$**8**: IR ($CHCl_3$) 3053, 2985, 2305, 1422, 1264 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.04 (m, 1H), 5.20-5.10 (m, 2H), 4.81 (d, 1H, J = 6.9 Hz), 4.73 (d, 1H, J = 2.37 Hz), 4.67 (d, 1H, J = 6.8 Hz), 3.62 (m, 2H), 3.55 (s, 3H), 2.47 (m, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 1.85 (m, 1H), 1.03 (d, 3H, J = 7.1 Hz), 0.97 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 135.1, 116.4, 101.3, 95.9, 81.9, 75.8, 56.4, 55.7, 37.5, 37.3, 33.6, 13.2, 9.9; HRMS (EI) calcd for $C_{13}H_{24}O_4$ 244.1596, found 244.1592. $\tilde{\alpha}$**8**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (m, 1H), 5.22-5.12 (m, 2H), 4.83 (d, 1H, J = 6.9 Hz), 4.69 (d, 1H, J = 7.2 Hz), 4.49 (d, 1H, J = 1.8 Hz), 3.88 (dt, 1H, J = 3.6, 8.8 Hz), 3.53 (t, 2H, J = 3.6 Hz), 3.48 (s, 3H), 2.45 (m, 1H), 2.28-2.11 (m, 3H), 1.94

(m, 1H), 1.12 (d, 3H, J = 7.3 Hz), 1.00 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 135.2, 116.7, 103.4, 95.6, 78.7, 69.6, 55.7, 37.2, 35.8, 33.6, 15.9, 13.5.

[0097] **(2*S*,3*R*,4*S*,5*R*,6*R*)-3-(6-Methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl)propionaldehyde (9a).** $BH_3.Me_2S$ (1 M in THF, 3 mL, 3 mmol) was added to a solution of **8** (488 mg, 2 mmol) in THF (10 mL) at 0 °C with stirring. The mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with 2N aqueous NaOH (10 mL) followed by H_2O_2 (30 %, 3 mL). After 1 h, the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and chromatographed (hexane/EtOAc 7:3) to yield 392 mg (75%) of alcohol as a colorless oil: IR ($CHCl_3$) 3103, 2982, 1375, 1240 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.83 (d, 1H, J = 6.9 Hz), 4.76 (d, 1H, J = 2.4 Hz), 4.69 (d, 1H, J = 6.9 Hz), 3.75 (t, 2H, J = 5.4 Hz), 3.61 (t, 1H, J = 2.7 Hz), 3.57 (s, 3H), 2.58 (br s, 1H), 2.17 (m, 1H), 1.90-1.80 (m, 4H), 1.04 (d, 3H, J = 7.1 Hz), 0.97 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 101.5, 96.0, 82.0, 75.9, 62.8, 56.6, 55.8, 37.6, 34.0, 29.4, 28.6, 13.4, 9.8; HRMS (EI) calcd for $C_{13}H_{26}O_5$ 262.1780, found 262.1792.

[0098] Pyridinium sulfurtrioxide (477 mg, 3 mmol) was added to a stirred solution of alcohol (262 mg, 1 mmol) and *N,N*-diisopropylethylamine (0.52 mL, 3 mmol) in anhydrous CH_2Cl_2 (6 mL) and DMSO (12 mL) at 0 °C. The reaction mixture was stirred at the ambient temperature for 1 h. The mixture was diluted with ethyl ether (50 mL) and washed with aqueous HCl (0.5 N, 50 mL) and brine (10 ml). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. Flash silica gel column chromatography filtration (hexane/EtOAc 4:1) to remove SO_3-pyridine residue provided the crude aldehyde **9a** as a colorless oil which was used without further purification.

[0099] **(4*R*)-4-Benzyl-3-[(2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-6-(4-methoxybenzyloxy)-2-methylhexanoyl]oxazolidin-2-one (11).** Pyridinium sulfur trioxide (7.15 g, 45 mmol) was added to a stirred solution of the mono-PMB-protected alcohol **10** (3.15 g, 15 mmol) and *N,N*-diisopropylethylamine (8.0 mL, 45 mmol) in anhydrous CH_2Cl_2 (15 mL) and DMSO (30 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h, diluted with ethyl ether (300 mL) and washed with aqueous HCl (0.5 N, 200 mL), and brine. The separated organic layer was dried over $MgSO_4$. Filtration and concentration provided the crude aldehyde **10** as a colorless oil which was used for the next reaction without further purification.

[00100] *N,N*-Diisopropylethylamine (1.9 mL, 11 mmol) was added to a solution of propionyloxazolidinone (2.33 g, 10 mmol) in anhydrous CH_2Cl_2 (110 mL) at 0 °C, followed by dropwise addition of Bu_2BOTf (1.0 M in CH_2Cl_2, 11 mL, 11 mmol). The solution was stirred for 0.5 h at 0 °C. Crude **10** in anhydrous CH_2Cl_2 (30 mL) was added at –78 °C. The mixture was stirred for 10 min at –78 °C followed by an additional 2 h at 0 °C. The reaction was quenched by addition of phosphate buffer, pH 7.0 (50 mL). A solution of hydrogen peroxide (30 %, 10 mL) in methanol (20 mL) was added and the mixture was allowed to stir for 1 h at 0 °C. After separation of organic and aqueous layers, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and chromatographed (hexane/EtOAc 4:1) to yield the aldol adduct (3.83 g, 87 %) as a colorless oil: IR ($CHCl_3$) 3472, 2954, 2860, 2252, 1778, 1691, 1383 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.36 (m, 7H), 7.01 (d, 2H, J = 8.7 Hz), 4.58 (m, 1H), 4.33 (s, 2H), 4.18 (br s, 1H), 3.94 (s, 3H), 3.91 (m, 1H), 3.63 (t, 2 H, J = 6.0 Hz), 3.40 (dd, 1H, J = 3.2, 13.3 Hz), 3,37 (br s, 1H), 2.90 (dd, 1H, J = 3.8, 13.3 Hz), 1.97-1.59 (m, 5H), 1.40 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 177.3, 159.2, 153.1, 135.3, 130.6, 129.5, 129.3, 129.0, 127.4, 113.8, 72.5, 71.5, 69.9, 66.2, 55.2, 42.7, 37.7, 31.3, 26.4, 14.3, 11.1; HRMS (EI) calcd for $C_{25}H_{31}NO_6$ 441.2151, found 441.2162.

[00101] TBDMSOTf (1.7 mL, 7.5 mmol) was added to a stirred solution of the above alcohol (2.20 g, 5 mmol) and 2,6-lutidine (1.2 mL, 10 mmol) in CH_2Cl_2 (50 mL) at –78 °C and the mixture was stirred for 2 h at ambient temperature. The reaction was quenched by addition of aqueous HCl (0.5 N, 100 mL). The reaction mixture was extracted with CH_2Cl_2 and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The product was purified by column chromatography (hexane/EtOAc 9:1) to yield **11**: IR ($CHCl_3$) 3020, 2955, 2858, 1779, 1362, 1211 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.36 (m, 7H), 7.00 (d, 2H, J = 8.7 Hz), 4.70 (m, 1H), 4.56 (s, 2H), 4.27-4.15 (m, 3H), 4.04 (dd, 1H, J = 5.4, 6.8), 3.91 (s, 3H), 3.60 (m, 3 H), 3.40 (dd, 1H, J = 3.0, 13.2 Hz), 2.90 (dd, 1H, J = 9.5, 13.2 Hz), 1.80 (br m, 4H), 1.38 (d, 3H, J = 6.8 Hz), 1.05 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.4, 159.2, 153.2, 135.5, 130.9, 129.6, 129.3, 129.0, 127.4, 113.8, 72.9, 72.5, 70.2, 66.1, 55.9, 55.3, 42.8, 37.7, 32.1, 26.0, 25.2, 18.2, 12.2, -3.92, -4.65; LRMS (ESI) 578.3 (M + Na).

[00102] **(2*S*,3*S*)-3-(*tert*-Butyldimethylsilanyloxy)-6-(4-methoxybenzyloxy)-2-methylhexan-1-ol.** Lithium borohydride (2.0 M in THF, 5 mL, 10 mmol) was added dropwise to a stirred solution of **11** (2.77 g, 5 mmol) and methanol (0.4 mL, 10 mmol) in

anhydrous THF (20 mL) under an atmosphere of N_2 at 0 °C. The mixture was stirred for 20 min at 0 °C and then warmed to ambient temperature. After 3 h at room temperature, the reaction was quenched with aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and chromatographed (hexane/EtOAc 7:3) to yield the alcohol (1.48 g, 78 %) as a colorless oil: IR ($CHCl_3$) 2948, 2856, 2302, 1612, 1265 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, 2H, *J* = 8.5 Hz), 7.00 (d, 2H, *J* = 8.5 Hz), 4.43 (s, 2H), 3.78 (s, 3H), 3.67 (dd, 1 H, *J* = 8.6, 10.5 Hz), 3.51-3.41 (m, 3H), 2.78 (br s, 1H), 1.94 (m, 1H), 1.72-1.49 (m, 4H), 0.90 (s, 9H), 0.81 (d, 3H, *J* = 7.0 Hz), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 130.6, 129.3, 113.8, 75.4, 72.6, 70.1, 65.8, 55.9, 55.3, 39.7, 29.1, 26.6, 25.9, 18.0, 12.1, –4.28, –4.38; LRMS (ESI) 405.2 (M + Na).

[00103] (4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*,5*S*)-5-(*tert*-butyldimethylsilanyloxy)-3-hydroxy-8-(4-methoxybenzyloxy)-2,4-dimethyloctanoyl]oxazolidin-2-one (12). Pyridinium sulfur trioxide (2.38 g, 15 mmol) was added to a stirred solution of the above TBS-protected alcohol (1.91 g, 5 mmol) and *N,N*-diisopropylethylamine (2.65 mL, 15 mmol) in anhydrous CH_2Cl_2 (5 mL) and DMSO (10 mL) at 0 °C. The mixture was stirred at the ambient temperature for 1 h, diluted with ethyl ether (100 mL), washed with aqueous HCl (0.5 N, 100 mL) and brine, then dried over $MgSO_4$. Filtration and concentration provided the crude aldehyde as a colorless oil which was used without further purification.

[00104] *N,N*-Diisopropylethylamine (0.97 mL, 5.5 mmol) was added to a solution of propionyloxazolidinone (1.16 g, 5 mmol) in anhydrous CH_2Cl_2 (11 mL) at 0 °C, followed by dropwise addition of Bu_2BOTf (1.0 M in CH_2Cl_2, 5.5 mL, 5.5 mmol). The solution was stirred for 0.5 h at 0 °C. A solution of crude aldehyde **12** from above in anhydrous CH_2Cl_2 (10 mL) was added at –78 °C. The reaction mixture was stirred for 10 min at –78 °C then for 2 h at 0 °C. The reaction mixture was quenched with phosphate buffer, pH 7.0 (50 mL). A solution of hydrogen peroxide (30 %, 10 mL) in methanol (20 mL) was slowly added and the mixture was stirred for 1 h. After the separation of organic and aqueous layers, the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and chromatographed (hexane/EtOAc 4:1) to yield desired compound (2.29 g, 75 %) as a colorless oil: IR ($CHCl_3$) 2949, 2855, 2253, 1779, 1692, 1463 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.19 (m, 7H), 7.01 (d, 2H, *J* = 8.1 Hz), 4.42 (m, 1H), 4.44 (s, 2H), 4.16 (d, 1H, *J* = 5.1 Hz), 4.01 (m, 1H), 3.95 (t, 1H, *J* = 6.3 Hz), 3.85 (m, 1H), 3.79 (s, 3 H), 3.43 (br s, 2H), 3,24 (br s, 1H), 3.20 (dd, 1H, *J* = 2.4, 13.5 Hz), 2.77 (dd, 1H, *J* = 9.6,

13.2 Hz), 1.56-1.31 (m, 5H), 1.32 (d, 3H, J = 6.9 Hz), 0.95 (d, 3H, J = 6,9 Hz), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 177.2, 159.2, 152.7, 135.1, 130.6, 129.5, 129.3, 129.0, 127.5, 113.8, 76.8, 74.2, 72.6, 70.0, 66.1, 55.3, 55.0, 40.6, 38.1, 37.8, 31.3, 25.9, 18.1, 13.2, 7.4, –3.5, –4.6; HRMS (EI) calcd for $C_{34}H_{51}NO_7Si$ 613.3435, found 613.3427.

[00105] (4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*,5*S*)-5-(*tert*-butyldimethylsilanyloxy)-8-(4-methoxybenzyloxy)-3-methoxymethoxy-2,4-dimethyloctanoyl]oxazolidin-2-one (13). *N,N*-Diisopropylethylamine (7.5 mL) and chloromethyl methyl ether (mL, 9 mmol) were added to a solution of the alcohol from above (1.83 g, 3 mmol) in CH_2Cl_2 (15 mL). The mixture was stirred at reflux overnight. The reaction was quenched with aqueous sat'd $NaHCO_3$ (50 mL) and washed with brine. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/EtOAc 4:1) to provide the pure product in 92% yield: IR ($CHCl_3$) 3020, 2862, 1781, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.27 (m, 7H), 6.94 (d, 2H, J = 8.7 Hz), 4.75 (s, 2H), 4.69 (m, 1H), 4.53 (s, 2H), 4.19 (dd, 1H, J = 10.2, 15.0 Hz), 3.97 (dd, 1H, J = 3.0, 6.6 Hz), 3.84 (br s, 4H), 3.43 (br t, 2H), 3,45 (s, 3H), 3.30 (dd, 1H, J = 3.0, 13.2 Hz), 2.77 (dd, 1H, J = 9.3, 13.5 Hz), 1.81-1.75 (m, 5H), 1.36 (d, 3H, J = 6.9 Hz), 1.02 (d, 3H, J = 6.9 Hz), 0.98 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.5, 159.1, 153.0, 135.4, 131.0, 129.5, 129.2, 129.0, 127.4, 113.7, 98.3, 80.3, 76.9, 73.2, 72.3, 70.5, 66.0, 56.3, 55.6, 55.2, 41.7, 40.8, 37.6, 30.6, 26.1, 24.2, 18.3, 14.0, 10.5, –3.9, –4.3; HRMS (EI) calcd for $C_{34}H_{50}NO_7Si$ (M–CH_2OCH_3) 612.3356, found 612.3367 (M–CH_2OCH_3).

[00106] 6-[(3*R*,4*S*,5*S*,6*S*)-3-(4-Methoxybenzyloxy)propyl]-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-one (14). HF-pyridine (6 mL) was added to a solution of **13** (1.31 g, 2 mmol) in MeOH (20 mL) and pyridine (10 mL) at 0 °C. The mixture was stirred at room temperature for 48 h, diluted with EtOAc (100 mL), washed with aqueous HCl (0.5 N, 2 x 50 mL) and with brine. The aqueous layer was extracted with EtOAc (50 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc 4:1) to provide the pure product in 83% yield: IR ($CHCl_3$) 3020, 2952, 1730, 1513, 1216 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 4.72 (d, 1H, J = 7.2 Hz), 4.60 (d, 1H, J = 7.2 Hz), 4.48 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.50-3.39 (m, 2H), 3.39 (s, 3H), 3.26 (dd, 1H, J = 1.1, 7.0 Hz), 2.58 (t, 1H, J = 6.9 Hz), 2.03 (d, 1H, J = 7.5 Hz), 1.81-1.63 (m, 4H), 1.31 (d, 3H, J = 6.7 Hz), 0.91 (d, 3H, J = 7.3

Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 174.1, 159.2, 130.5, 129.3, 113.8, 95.5, 82.6, 76.7, 72.6, 69.4, 55.9, 55.3, 40.5, 38.4, 28.6, 26.0, 14.4, 11.9, –3.9; HRMS (EI) calcd for $C_{20}H_{30}O_6$ 366.2042, found 366.2050.

[00107] 2-Methoxy-6-[(3*R*,4*S*,5*S*,6*S*)-3-(4-methoxybenzyloxy)propyl]-4-methoxymethoxy-3,5-dimethyltetrahydropyran (15). Diisobutylaluminum hydride (1.0 M in THF, 2.2 mL, 2.2 mmol) was added dropwise to a stirred solution of **14** (732 mg, 2 mmol) in anhydrous CH_2Cl_2 (20 mL) under an atmosphere of N_2 at –78 °C and the mixture was stirred for 1 h at –78 °C. The reaction was quenched by the careful addition of aqueous sat'd potassium sodium tartrate (50 mL) and stirring for 3 h at room temperature. Once the organic and aqueous layers separated, the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of solvent under reduced pressure. The crude lactol obtained was used without further purification.

[00108] A solution of the lactol and PPTS (0.2 mmol) in MeOH was stirred for 15 h at room temperature. The reaction mixture was diluted with EtOAc (100 mL) and washed with sat'd aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane/EtOAc 7:3) to provide the pure product each anomer **15** (β, 64%; α, 26 %). **β-15**: IR ($CHCl_3$) 3020, 2858, 2299, 1514, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 2H, J = 8.7 Hz), 6.95 (d, 2H, J = 8.7 Hz), 4.76 (d, 2H, J = 3.0 Hz), 4.52 (s, 2H), 4.37 (d, 1H, J = 4.6 Hz), 4.09 (m, 1H), 3.89 (s, 2H), 3.57 (m, 2H), 3.47 (s, 3H), 3.32 (t, 1H, J = 5.7 Hz), 1.89-1.71 (m, 6H), 1.16 (d, 3H, J = 7.2 Hz), 1.07 (d, 3H, J = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 130.7, 129.3, 113.8, 103.2, 96.3, 82.0, 72.6, 69.9, 69.3, 55.7, 55.3, 39.1, 38.0, 27.1, 26.5, 16.0, 13.1; HRMS (EI) calcd for $C_{21}H_{34}O_6$ 382.2353, found 382.2355. **α-15**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, 2H, J = 8.7 Hz), 6.95 (d, 2H, J = 8.7 Hz), 4.72 (s, 2H), 4.70 (d, 1H, J = 2.8 Hz), 4.52 (s, 2H), 4.09 (br m, 4H), 3.67 (br s, 1H), 3.56 (m, 5H), 3.44 (s, 3H), 2.08-1.54 (m, 6H), 1.11 (d, 3H, J = 3.0 Hz), 1.08 (d, 3H, J = 2.9 Hz).

[00109] (2*S*,3*S*,4*S*,5*R*,6*R*)-3-(6-Methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl)propionaldehyde (9b). A mixture of PMB ether **15** (458 mg, 1.2 mmol) and palladium (10 % Pd/C, 5 mg) was stirred in EtOAc (12 mL) for 3 h at room temperature under an H_2 atmosphere (balloon), filtered and concentrated to yield the debenzylated alcohol which was used without further purification.

[00110] The crude alcohol in CH_2Cl_2 (12 mL) was treated with Dess-Martin periodinane (636 mg, 1.5 mmol) at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography (hexane/EtOAc 4:1) provided 274 mg (88%) of the crude aldehyde as a colorless oil which was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 4.67 (dd, 2H, J = 7.0, 12.5 Hz), 4.27 (d, 1H, J = 4.5 Hz), 3.99 (dd, 1H, J = 3.5, 4.0 Hz), 3.36 (s, 6H), 3.24 (t, 1H, J = 6.0 Hz), 2.61 (m, 1H), 2.52 (m, 1H), 1.83 (m, 3H), 1.68 (m, 1H), 1.05 (d, 3H, J = 7.0 Hz), 1.01 (d, 3H, J = 7.5 Hz).

[00111] **(2*S*,3*R*,4*S*)-5-(*tert*-Butyldimethylsilanyloxy)-2,4-dimethylpentane-1,3-diol.** MeOH (0.51 mL) and $LiBH_4$ (2.0 M in THF, 6.2 mL, 12.4 mmol) were added dropwise to a stirred solution of aldol product **18** [22] (5.38 g, 12.3 mmol) in THF (50 mL) at 0 ^{O}C. After stirring for 1 h at 0 ^{O}C, saturated aqueous sodium potassium tartrate (70 mL) was added. The mixture was allowed to warm room temperature and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with brine (40 mL), dried over anhydrous $MgSO_4$, concentrated and flash column chromatographed (hexane/EtOAc 4:1) to yield 2.99 g (92 %) of the desired product as a colorless oil: IR ($CHCl_3$) 3409, 2958, 2927, 2853, 2878, 1469, 1385, 1361, 1252, 1082, 838, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (br s, 1H), 3.54 (br s, 1H), 1.92 (m, 1H), 1.83 (m, 1H), 1.06 (d, 3H, J = 6.98 Hz), 1.00 (s, 9H), 0.84 (d, 3H, J = 6.88 Hz), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 79.3, 69.7, 67.5, 37.4, 36.6, 25.9, 18.1, 12.8, 8.9, –5.5, –5.6; LRMS (EI) 263 (M+H); HRMS (EI) calcd for $C_{13}H_{30}O_3Si$ 263.2042, found 263.2042; $[\alpha]^{20}_D$ +35.5 (*c* 0.85, $CHCl_3$).

[00112] **(2*S*)-*tert*-Butyl-{(4*R*,5*S*)-2-[2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]propoxy}dimethylsilane (20).** A solution of the above diol (2.8 g, 10.7 mmol), *p*-anisaldehyde dimethylacetal (2.0 mL, 11.7 mmol) and PPTS (0.27 g, 1.1 mmol) in benzene was heated to reflux for 3 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc 9:1) to give **20** (2.6 g, 6.8 mmol) in 64% yield: IR ($CHCl_3$) 2955, 2927, 2853, 1617, 1518, 1459, 1382, 1157, 1101, 1033, 826 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (m, 2H), 6.98 (m, 2H), 5.50 (m, 2H), 3.89 (s, 3H), 3.82 (dd, 1H, J = 10.9, 4.9 Hz), 3.76 (dd, 2H, J = 8.1, 2.8 Hz), 1.87 (m, 1H), 1.71 (m, 1H), 1.23 (d, 3H, J = 7.6 Hz), 1.00 (d, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 160.1, 132.1, 127.6, 113.8, 113.7, 101.9, 80.1, 74.3, 65.2, 64.3, 55.5, 37.4, 30.0, 26.3, 26.2, 18.7, 12.4, 11.3, –5.0, –5.1; LRMS (EI) 323, 207, 187, 157, 145, 121, 75; HRMS (EI) calcd

for $C_{21}H_{36}O_4Si_1$ 323.1678 (M – ^{t}Bu), found 323.1694 (M – ^{t}Bu); $[\alpha]^{20}_D$ –33.6 (*c* 1.24, $CHCl_3$).

[00113] (2*S*)-2-[(4*R*,5*S*)-2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]propan-1-ol. TBAF (1.0M in THF, 22 mL, 22 mmol) was added to a solution of **20** (2.8 g, 7.3 mmol) in THF (70 mL) at room temperature and the mixture was stirred for 2 h. The mixture was diluted with ethyl ether (100 mL) and brine. The organic layer was dried over $MgSO_4$. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 7:3) provided alcohol (1.95 g, 7.2 mmol) as a yellow oil: IR ($CHCl_3$) 3428, 2964, 2930, 2835, 1614, 1512, 1463, 1391, 1249, 1098, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m 2H), 6.87 (m, 2H), 5.48 (s, 1H), 4.11 (dd, 2H, *J* = 4.6, 4.5 Hz), 3.75 (s, 3H), 3.73 (m, 2H), 3.52 (apparent t, 1H, *J* = 11.1 Hz), 2.08 (m, 1H), 2.00 (m, 1H), 1.04 (d, 3H, *J* = 7.1 Hz), 0.77 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 160.0, 131.5, 127.4, 113.6, 101.6, 83.4, 73.9, 66.3, 55.2, 36.8, 30.4, 11.9, 9.9; LRMS (EI) 266, 207, 177, 153, 135, 77; HRMS (EI) calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1517; $[\alpha]^{20}_D$ –4.8 (*c* 0.67, $CHCl_3$).

[00114] (2S)-{2-[(4R,5S)-2-(4-Methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]propyl}triphenyl-□5-phosphane iodide (21). I_2 (4.48 g, 17.6 mmol) was added at 0 °C to a solution of the alcohol from above (2.35 g, 8.82 mmol) in CH_2Cl_2 (110 mL) containing imidazole (1.32 g, 19.4 mmol) and triphenylphosphine (4.63 g, 17.6 mmol). The resulting slurry was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$(10 mL). The organic layer was separated and washed with water (20 mL), brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc 9:1) to give the pure iodide.

[00115] The iodide was quickly dissolved in benzene (44 mL), PPh_3 was added (11.5 g, 44.1 mmol) and the mixture heated to reflux for 36 h. The reaction mixture was cooled to room temperature and anhydrous ethyl ether (50 mL) was added, whereupon a white solid precipitated. Filtration followed by washing of the solid with ethyl ether (10 mL) provided the phosphonium salt (4.5 g) as a white foam: IR ($CHCl_3$) 3054, 2961, 2909, 1611, 1515, 1435, 1246, 1107, 993, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 9H), 7.37 (m, 6H), 7.21 (m, 2H), 6.65 (m, 1H), 5.41 (s, 1H), 3.95 (d, 1H, *J* = 10.2 Hz), 3.68 (d, 2H, *J* = 12.3 Hz), 3.54 (s, 3H), 3.26 (m, 1H), 1.85 (m, 1H), 1.46 (apparent d, 1H, *J* = 6.5 Hz), 0.78 (d, 3H, *J* = 6.8 Hz), 0.44 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 160.0, 135.2, 135.1, 133.7, 133.5, 131.1, 130.5, 130.4, 127.9, 119.0, 117.9, 113.5, 101.9, 82.3, 82.1, 73.2, 55.5, 30.7,

29.2, 25.3, 15.7, 10.4 HRMS (EI) calcd for $C_{33}H_{36}O_3P$ 511.2402, found 511.2428; $[\alpha]^{20}_D$ +31.9 (*c* 0.78, $CHCl_3$).

[00116] (4*R*,5*R*)-*tert*-Butyl-{3-[2-(4-methoxyphenyl)-5-methyl[1,3]dioxan-4-yl]propoxy}dimethylsilane (26). Lithium borohydride (2.0 M in THF, 25 mL, 50 mmol) was added dropwise to a stirred solution of **25** (8.70 g, 20 mmol) and MeOH (1.61 mL, 40 mmol) in anhydrous THF (100 mL) under an atmosphere of N_2 at 0 °C. The mixture was stirred for 20 min at 0 °C and then warmed to ambient temperature. After 2 h at room temperature, the reaction was quenched with aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and chromatographed (hexane/EtOAc 7:3) to yield 4.97 g (95%) of the diol as a colorless oil.

[00117] A solution of the diol (2.62 g, 10 mmol), anisaldehyde dimethyl acetal (2.00 g, 11.0 mmol), and PPTS (0.1 equiv) in benzene was stirred for 15 h at reflux. The reaction mixture was quenched with aqueous sat'd $NaHCO_3$ (50 mL) followed by washing with water. The aqueous layer was extracted with ethyl ether (2 x 50 mL) . The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc 7:3) to provide the pure **26** in 72% yield: IR ($CHCl_3$) 2992, 1742, 1373, 1240 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, 2H, *J* = 8.4 Hz), 6.88 (d, 2H, *J* = 8.4 Hz), 5.45 (s, 1H), 4.08 (dd, 2H, *J* = 10.5, 29.9 Hz), 3.90 (br s, 1H), 3.80 (s, 3H), 3.67 (m, 2H), 1.67-1.50 (m, 5H), 1.17 (d, 3H, *J* = 7.0 Hz), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.9, 131.6, 127.4, 113.6, 101.7, 79.7, 73.9, 63.1, 55.3, 31.8, 29.3, 28.7, 26.0, 18.4, 11.1, –5.1; LRMS (ESI) 402.68 (M + Na).

[00118] (4*R*,5*S*)-4-{(1*S*,2*Z*)-5-[(2*S*,3*R*,4*S*,5*R*,6*R*)-6-Methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-1-methylpent-2-enyl}-2-(4-methoxyphenyl)-5-methyl[1,3]dioxane (35). NaHMDS (1.0 M in THF, 1.1 mL, 1.1 mmol) was slowly added to a solution of the salt **21** (701 mg, 1.1 mmol) in dry THF (2.2 mL) at 0 °C. The resulting red solution was stirred at room temperature for 20 min. The mixture was cooled to –78 °C and a solution of the aldehyde **9a** (260 mg, 1 mmol) in THF (1 mL x 2) was added dropwise. The mixture was stirred for 20 min at –78 °C and then warmed to room temperature. After 4 h at room temperature, the mixture was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and chromatographed (hexane/ether 9:1) to yield 329 mg (67 %) of **35** as a colorless oil: IR ($CHCl_3$) 2922, 2866, 2628, 2350, 1740, 1516 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 7.45 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.4 Hz), 5.46 (m, 2H), 5.30 (t, 1H, J = 9.9 Hz), 4.77 (d, 1H, J = 6.9 Hz), 4.70 (d, 1H, J = 1.8 Hz), 4.63 (d, 1H, J = 6.9 Hz), 4.06 (br d, 1H, J = 2.1 Hz), 3.80 (s, 3H), 3.54 (m, 3H), 3.43 (s, 3H), 3.32 (s, 3H), 2.77 (m, 1H), 2.31 (dd, 2H, J = 7.5, 14.7 Hz), 1.79-1.55 (m, 4H), 1.22 (d, 3H, J = 6.6 Hz), 1.02 (d, 3H, J = 7.2 Hz), 0.96 (d, 3H, J = 6.9 Hz), 0.86 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 133.4, 131.8, 130.1, 127.3, 113.3, 101.5, 101.3, 95.9, 83.5, 82.0, 75.2, 73.9, 56.4, 55.7, 55.2, 37.6, 34.2, 33.6, 33.0, 30.0, 23.4, 16.1, 13.3, 11.2, 9.9; HRMS (EI) calcd for $C_{27}H_{40}O_6$ 460.2824, found 460.2846.

[00119] (4*R*,5*S*)-4-{(1*S*,2*Z*)-5-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-Methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-1-methylpent-2-enyl}-2-(4-methoxyphenyl)-5-methyl[1,3]dioxane (36). NaHMDS (1.0 M in THF, 1.1 mL, 1.1 mmol) was slowly added to a solution of the salt **21** (0.70 g, 1.1 mmol) in dry THF (2 mL) at 0 °C. The resulting red solution was stirred at room temperature for 20 min. The mixture was cooled to –78 °C and a solution of the aldehyde **9b** (260 mg, 1 mmol) in THF (1 mL) was added dropwise. The mixture was stirred for 20 min at –78 °C and then warmed to room temperature. After 4 h at room temperature, the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and chromatographed (hexane/ether 9:1) to yield 329 mg (67%) of **36** as a colorless oil: IR ($CHCl_3$) 2922, 2866, 2628, 2350, 1740, 1516 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 2H, J = 9.0 Hz), 6.91 (d, 2H, J = 9.0 Hz), 5.46 (m, 2H), 5.32 (t, 1H, J = 9.6 Hz), 4.73 (s, 2H), 4.31 (d, 1H, J = 5.4 Hz), 4.07 (br s, 2H), 3.81 (s, 1H), 3.57 (dd, 1H, J = 1.8, 9.6 Hz), 3.45 (s, 3H), 3.43 (s, 3H), 3.20 (t, 1H, J = 6.6 Hz), 2.77 (m, 1H), 2.31-2.17 (m, 2H), 1.90-1.62 (m, 4H), 1.24-0.98 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 133.7, 131.7, 129.4, 127.2, 113.4, 102.8, 101.5, 96.6, 83.5, 82.2, 73.9, 70.0, 55.7, 55.2, 39.8, 38.4, 33.6, 30.0, 29.9, 24.3, 15.9, 15.5, 13.2, 11.1; HRMS (EI) calcd for $C_{27}H_{40}O_6$ (M–$HOCH_3$) 460.2824, found 460.2846.

[00120] (2*R*,3*S*,4*S*,5*Z*)-3-(4-Methoxybenzyloxy)-8-[(2*S*,3*R*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,4-dimethyloct-5-enal (37). DIBAL (1.0 M in hexane, 2.1 mL, 2.1 mmol) was added dropwise to a solution of the acetal **35** (329 mg, 0.67 mmol) in dry CH_2Cl_2 (6.7 mL) at 0 °C. After stirring for 2 h, the reaction was quenched with saturated aqueous sodium tartrate (20 mL) followed by vigorously stirring for several hours. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (10 mL). The residue obtained after drying

over $MgSO_4$ and evaporation under vacuum was dissolved in anhydrous CH_2Cl_2 (6 mL) and DMSO (12 mL), treated with *N,N*-diisopropylethylamine (0.52 mL, 3 mmol), cooled to 0 °C and treated with pyridinium sulfur trioxide (477 mg, 3 mmol). The reaction mixture was stirred at ambient temperature for 1 h, diluted with ethyl ether (50 mL) and washed with aqueous HCl (0.5 N, 50 mL) and brine (10 ml). The separated organic layer was dried over $MgSO_4$. Filtration and concentration followed by short flash column chromatography (hexane/EtOAc 4:1) provided the crude aldehyde **37** (270 mg, 0.55 mmol) as a colorless oil which was used without further purification.

[00121] (2*R*,3*S*,4*S*,5*Z*)-3-(4-Methoxybenzyloxy)-8-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,4-dimethyloct-5-enal (38). DIBAL (1.0 M in hexane, 2.1 mL, 2.1 mmol) was added dropwise to a solution of the acetal 36 (329 mg, 0.67 mmol) in dry CH_2Cl_2 (6.7 mL) at 0 °C. After the mixture was stirred for 2 h, the reaction was quenched with saturated aqueous sodium tartrate (20 mL) followed by vigorous stirring for several hours. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, the residue was used for the next reaction without further purification. The crude alcohol in CH_2Cl_2 (13 mL) was treated with Dess-Martin periodinane (340.8 mg, 0.80 mmol). After the reaction was complete, the mixture was quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 9:1) provided crude aldehyde 38 (267 mg, 81%) as a colorless oil which was used without further purification.

[00122] **(2*S*,3*R*)-6-(*tert*-Butyldimethylsilanyloxy)-3-(4-methoxybenzyloxy)-2-methylhexanal (27).** DIBAL (1.0 M in THF, 15 mL, 15 mmol) was added dropwise to a stirred solution of **26** (1.90 g, 5 mmol) in anhydrous CH_2Cl_2 (50 mL) under an atmosphere of N_2 at 0 °C and the mixture was stirred for 1 h at 0 °C. The reaction was quenched by the careful addition of aqueous sat'd potassium sodium tartrate(100 mL) and stirring for 3 h at room temperature. Once the aqueous and organic layers separated, the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The crude alcohol (1.56 g, 4.1 mmol) was used without further purification.

[00123] Pyridinium sulfur trioxide (2.38 g, 15 mmol) was added to a stirred solution of the crude alcohol from above and diisopropylethylamine (2.6 mL, 15 mmol) in anhydrous

CH_2Cl_2 (10 mL) and DMSO (20 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h. After the reaction was complete, the mixture was diluted with ethyl ether (100 mL) and washed with aqueous HCl (0.5 N, 100 mL) and brine (100 ml). The separated organic layer was dried over $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 4:1) to remove SO_3-pyridine provided the crude aldehyde **27** as a colorless oil which was used without further purification.

[00124] **(2*R*,3*R*,4*R*,5*R*)-8-(*tert*-Butyldimethylsilanyloxy)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethyloctanoic acid, 2,6-dimethylphenyl ester (29).** LDA (2M in THF, 3.1 mL, 6.2 mmol) was added to a solution of 2,6-dimethylphenoxy propionate (1.10 g, 6.2 mmol) in anhydrous THF (12.4 mL) at –78 °C, followed by stirring for 1 h at –78 °C. The crude aldehyde **27** (4.1 mmol) from above dissolved in anhydrous THF (10 mL) was added slowly at -78 °C. After 2 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, evaporated and chromatographed (hexane/EtOAc 4:1) to yield **29** (1.67 g, 2.99 mmol) as a colorless oil: IR ($CHCl_3$) 3120, 2857, 1744, 1514, 1216, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, 2H, J = 8.4 Hz), 6.87 (d, 2H, J = 8.4 Hz), 4.62 (d, 1H, J = 11.1 Hz), 4.40 (d, 1H, J = 11.1 Hz), 4.06 (d, 1H, J = 6.8 Hz), 3.79 (s, 3H), 3.66-3.61 (m, 3H), 2.89 (m, 1H), 2.19 (s, 6H), 1.86 (m, 2H), 1.55 (m, 3H); 1.27 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.9 Hz), 0.93 (s, 9 H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 159.2, 148.0, 130.0, 129.9, 129.4, 128.4, 125.6, 113.8, 83.5, 70.7, 62.9, 55.1, 44.0, 35.6, 28.7, 26.6, 25.8, 18.2, 16.3, 14.2, 5.7, -5.3; HRMS (EI) calcd for $C_{32}H_{50}O_6Si$ 558.3377, found 558.3392.

[00125] **(2S,3S,4R,5R)-3,8-Bis-(*tert*-butyldimethylsilanyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethyloctan-1-ol.** TBDMSOTf (0.68 mL, 3 mmol) was added to a stirred solution of **29** (1.11 g, 2 mmol) and 2,6-lutidine (0.69 mL, 6 mmol) in CH_2Cl_2 (20 mL) at –78 °C. The mixture was stirred for 2 h at ambient temperature. The reaction was quenched by the addition of aqueous HCl (0.5 N, 50 mL). The reaction mixture was extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent was removed under reduced pressure. Short column chromatography (hexane/EtOAc 4:1) provided the crude product.

[00126] DIBAL (1.0 M in THF, 6 mL, 6 mmol) was added dropwise to a stirred solution of the TBS-protected aryl ester (1.90 g, 2 mmol) from above in anhydrous CH_2Cl_2 (20 mL) under an atmosphere of N_2 at 0 °C and the mixture was stirred for additional 1 h at 0 °C. The reaction was quenched by the careful addition of aqueous sat'd potassium sodium

tartrate (50 mL). The mixture was stirred for 3 h at room temperature. Once the aqueous and organic layers had separated, the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane/EtOAc 3:7) to give pure (997 mg, 1.8 mmol): IR ($CHCl_3$) 3125, 1544, 1289, 1065 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, 2H, J = 8.7 Hz), 6.89 (d, 2H, J = 8.7 Hz), 4.51 (d, 1H, J = 11.1), 4. 41 (d, 1H, J = 10.8 Hz), 3.83 (d, 3H), 3.79 (m, 1H), 3.64 (m, 4H), 3.36 (m, 1H), 2.45 (br s, 1H), 1.93 (m, 2H), 1.63 (m, 4H), 1.00 (d, 2H, J = 7.0 Hz), 0.92 (s, 24H), 0.14 (s, 6H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.6, 129.4, 113.6, 80.3, 76.0, 71.2, 65.2, 63.0, 55.1, 39.1, 39.0, 29.0, 27.1, 26.1, 25.9, 18.2, 14.5, 11.6, –3.6, –3.9, –5.3; LRMS (ESI) 576.8 (M+ Na).

[00127] (2*R*,3*S*,4*R*,5*R*)-3,8-Bis-(*tert*-butyldimethylsilanyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethyloctanal (30). Pyridinium sulfurtrioxide (858 mg, 5.4 mmol) was added to a stirred solution of alcohol (997 mg, 1.8 mmol) from above and diisopropylethylamine (0.94 mL, 5.4 mmol) in anhydrous CH_2Cl_2 (3.6 mL) and DMSO (7.2 mL) at 0 °C. The mixture was stirred at ambient temperature for 1 h. After the reaction was complete, the mixture was diluted with ethyl ether (50 mL) and washed with aqueous HCl (0.5N, 50 mL) and brine (10 ml). The organic layer was dried over $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 4:1) to remove SO_3-pyridine provided the crude aldehyde **30** as a colorless oil which was used without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.22 (d, 2H, J = 8.6 Hz), 6.85 (d, 2H, J = 8.6 Hz), 4.45 (d, 1H, J = 11.1 Hz), 4.28 (d, 1H, J = 11.1 Hz), 3.94 (dd, 1H, J = 5.5, 4.0 Hz), 3.79 (s, 3H), 3.60 (t, 2H, J = 6.0 Hz), 3.40-3.34 (m, 1H), 2.66-2.58 (m, 1H), 1.92-1.84 (m, 1H), 1.67-1.59 (m, 2H), 1.55-1.45 (m, 2H), 1.02 (d, 3H, J = 7.0 Hz), 0.98 (d, 3H, J = 7.0 Hz), 0.89 (s, 9H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 9H).

[00128] (1*R*,2*R*,3*S*,4*S*,5*Z*)-1-{3-(*tert*-Butyldimethylsilanyloxy)-1-[3-(*tert*-butyldimethylsilanyloxy)propyl]-2,4-dimethylocta-5,7-dienyloxymethyl}-4-methoxybenzene (32). $CrCl_2$ (1.09 g, 9.0 mmol) was added to a stirred solution of the crude aldehyde (1.8 mmol) from above and 1-bromoallyl trimethylsilane **31** (578 mg, 5.4 mmol) in anhydrous THF (18 mL) under an atmosphere of N_2 at room temperature. The mixture was stirred for 14 h at ambient temperature, then diluted with ethyl ether followed by filtration through Celite. After the evaporation of the solvent under reduced pressure, the residue was

purified by short silica gel column chromatography (CH_2Cl_2). The resulting residue was used without further purification.

[00129] The above product in THF (50 mL) was cooled to 0 °C and NaH (95 % w/w, 207 mg, 9.0 mmol) was added in one portion. The ice bath was removed after 15 min and the mixture was stirred for 2 h at ambient temperature. The reaction mixture was cooled to 0 °C, quenched with H_2O (10 mL) and extracted with ethyl ether (2 x 50 mL). The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 4:1) to give pure **32** (622 mg, 1.2 mmol): IR ($CHCl_3$) 2954, 2931, 2857, 1608, 1513, 1463, 1251, 1098, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 2H, J =8.6 Hz), 6.96 (d, 2H, J = 8.6 Hz), 6.41 (ddd, 1H, J = 16.7, 11.0, 10.1 Hz), 6.04 (dd, 1H, J =11.1, 11.0 Hz), 5.57 (dd, 1H, J = 10.1, 16,8 Hz), 5.20 (d, 1H, J =16.7 Hz), 5.06 (d, 1H, J = 10.1 Hz), 4.51 (d, 1H, J = 11.3 Hz), 4.35 (d, 1H, J = 11.3 Hz), 3.81 (s, 3H), 3.63-3.57 (m, 3H), 3.28 (dt, 1H, J =5.5, 5.5 Hz), 2.70 (ddq, 1H, J = 10.3, 6.9, 3.2 Hz), 1.73-1.58 (m, 3H), 1.50-1.44 (m, 2H), 0.94 (d, 3H, J = 6.9 Hz), 0.93-0.91 (m, 21H), 0.06 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.1, 134.8, 132.5, 131.0, 129.5, 128.9, 117.1, 113.7, 78.9, 76.6, 70.7, 63.2, 55.2, 40.0, 36.4, 31.6, 28.7, 26.2, 26.0, 18.9, 18.5, 18.3, 10.9, -3.3, -3.4, -5.3; LRMS (EI) 576, 519, 467, 387, 357, 293, 225, 121; HRMS (EI) calcd for $C_{29}H_{51}O_4Si_2$ 519.3326, found 519.3332; $[\alpha]^{20}_D$ –18.8° (c 0.75, $CHCl_3$).

[00130] **(2*R*)-2-{(4*R*,5*S*,6*R*)-6-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-2,2,5-trimethyl[1,3]dioxan-4-yl}-propionic acid, 2,6-dimethylphenyl ester (34).** A mixture of PMB ether **29** (55.8 mg, 0.1 mmol) and palladium (10 % Pd/C, 5 mg) in EtOAc (10 mL) was stirred at room temperature under an H_2 atmosphere (balloon) for 3 h. The mixture was filtered and concentrated to yield the diol which was used without further purification. A solution of the crude diol, dimethyl dimethyl acetal (12.4 mg, 0.12 mmol) and PPTS (0.1 equiv.) in benzene was stirred for 5 h at 65 °C. The reaction was quenched with aqueous sat'd $NaHCO_3$ (50 mL) followed by washing with water. The aqueous layer was extracted with ethyl ether (2 x 50 mL). The combined organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane/EtOAc 9:1) to provide the pure **34** in 52% yield: IR ($CHCl_3$) 2855, 1742, 1510, 1091 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.03 (br s, 3H), 4.20 (dd, 1H, J = 1.7, 10.2 Hz), 3.91 (m, 1H), 3.64 (m, 2H), 2.91 (dq, 1H, J = 10.2, 6.9 Hz), 2.16 (s, 6H), 1.59-1.32 (m, 6H), 1.41 (s, 3H), 1.39 (s, 3H), 1.24 (d, 3H, J = 4.2 Hz), 0.92 (br s, 12H), 0.06 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) 173.7, 148.2, 130.3, 128.5, 125.8, 99.1, 75.2, 73.0, 63.1, 42.3, 31.8, 29.9, 29.3, 28.8, 26.0, 19.5, 18.4, 16.4, 12.9, 4.54, -5.19; HRMS (EI) calcd for $C_{27}H_{46}O_5Si$ 478.3115, found 463.2889 ($M-CH_3$).

[00131] **(1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-[3,9-Bis-(4-methoxybenzyloxy)-14-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl)tetradeca-6,11-dienyloxy]-*tert*-butyldimethylsilane**. NaHMDS (1.0 M in THF, 0.54 mL, 0.54 mmol) was added slowly to a solution of the salt **33** (475.9 mg, 0.54 mmol) in dry THF (1.08 mL) at 0 °C. The mixture was cooled to –78 °C and a solution of the aldehyde **38** (267 mg, 0.54 mmol) in THF (0.54 mL x 2) was added dropwise. The mixture was stirred for 20 min at –78 °C and then warmed to room temperature. After 4 h at room temperature the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$, evaporated and chromatographed (hexane/EtOAc 9:1) to yield the desired compound (257 mg, 0.28 mmol) as a colorless oil: IR ($CHCl_3$) 2920, 2861, 2620, 1740, 1520 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) 7.38 (m, 4H), 6.96 (m, 4H), 6.47 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.04 (t, 1H, J = 11.1 Hz), 5.57 (t, 1H, J = 10.5 Hz), 5.49-5.12 (m, 6H), 4.75 (d, 2H, J = 2.1 Hz), 4.67-4.33 (m, 5H), 4.07 (m, 1H), 3.65 (dd, 1H, J = 3.3, 6.0 Hz), 3.47 (br s, 7H), 3.35 (dd, 1H, J = 4.5, 4.7 Hz), 3.27 (t, 1H, J = 6.6 Hz), 3.15 (dd, 1H, J = 4.5, 6.9 Hz), 2.77 (m, 3H), 2.18 (m, 2H), 1.91 (m, 2H), 1.74-1.62 (m, 4H), 1.11-0.99 (m, 18H), 0.12 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 159.0, 134.7, 133.7, 132.9, 132.5, 131.4, 131.0, 129.6, 129.1, 128.9, 128.6, 117.3, 113.8, 113.7, 103.0, 96.5, 88.0, 82.1, 78.8, 74.9, 70.8, 69.7, 55.8, 55.3, 40.0, 39.5, 38.3, 35.6, 35.4, 31.3, 30.3, 26.4, 24.2, 23.7, 19.0, 18.8, 18.6, 17.3, 15.7, 13.2, 11.0, -3.1, -3.2; LRMS (ESI) 942.5 (M + Na).

[00132] **Carbamic acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-bis-(4-methoxybenzyloxy)-14-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl ester (39)**. The above compound (128.5 mg, 0.14 mmol) in THF (4 mL) was treated with TBAF (1.0 M in THF, 0.40 mL, 0.40 mmol) and the mixture was stirred at room temperature for 48 h. The mixture was diluted with ethyl ether (30 mL) and washed with water (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, the resulting alcohol was used without further purification.

[00133] A solution of the alcohol in CH_2Cl_2 (8 mL) at 0°C was treated with trichloroacetylisocyanate (0.05 mL, 0.42 mmol) and stirred at room temperature. After 30 min, the solution was concentrated under reduced pressure and the residue was taken up in

MeOH (4 mL). K_2CO_3 (50 mg) was added to this solution and the mixture was stirred at room temperature for 3 h at room temperature. The mixture was diluted with EtOAc (30 mL). The organic layer was washed with brine. The aqueous layer was extracted with EtOAc, and the combined extracts were dried over anhydrous Na_2SO_4. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 3:2) provided carbamate **39** (84.9 mg, 72%) as a yellow oil: IR ($CHCl_3$) 3100, 3019, 2430, 2286, 1720, 1524 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.41 (m, 4H), 7.01 (m, 4H), 6.46 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.11 (t, 1H, J = 10.8 Hz), 5.62 (t, 1H, J = 10.5 Hz), 5.53-5.18 (m, 6H), 4.94 (t, 1H, J = 6.0 Hz), 4.84 (br s, 2H), 4.81 (d, 2H, J = 2.1 Hz), 4.71-4.45 (m, 4H), 4.39 (d, 1H, J = 5.1 Hz), 4.12 (m, 1H), 3.37 (m, 2H), 3.19 (dd, 1H, J = 4.5, 6.9 Hz), 2.90 (m, 3H), 2.27 (m, 2H), 1.91 (m, 2H), 1.74-1.61 (m, 4H), 1.11-0.99 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) 159.2, 159.0, 157.1, 133.7, 133.3, 132.8, 132.2, 131.4, 130.9, 129.8, 129.6, 129.1, 128.5, 117.8, 113.8, 113.7, 102.9, 96.5, 88.0, 82.1, 78.4, 78.1, 74.9, 70.5, 69.8, 55.8, 55.7, 55.3, 39.5, 38.2, 37.7, 35.8, 35.4, 34.3, 30.6, 30.3, 24.2, 23.6, 18.9, 17.8, 17.4, 15.7, 13.2, 9.8; LRMS (ESI) 888.4 (M+K).

[00134] Carbamic acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-bis-(4-methoxybenzyloxy)-14-[(2*S*,3*S*,4*S*,5*R*)-4-methoxymethoxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-2,8,10–trimethyl-1-[(1S,2Z)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl ester. A solution of 39 (42.4 mg, 0.05 mmol) in THF (0.5 mL) and 60 % aqueous acetic acid (2.5 mL) was stirred at 70 °C for 4 h. After the reaction was complete by TLC, the mixture was neutralized slowly with saturated aqueous K_2CO_3 and diluted with EtOAc (20 mL). The aqueous phase was extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The crude lactol was used for the next reaction without further purification.

[00135] Dess-Martin periodinane reagent (31.8 mg, 0.075 mmol) was added to a solution of the lactol in CH_2Cl_2 (5 mL). The resultant solution was stirred for 1 h and quenched by the simultaneous addition of saturated aqueous $Na_2S_2O_3$ (5 mL) and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by flash column chromatography (hexane/EtOAc 8:2) provided 28.3 mg (68%) of the lactone as a colorless oil: IR ($CHCl_3$) 2992, 2361, 2332, 1742, 1374, 1242, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.40 (m, 4H), 7.03 (m, 4H), 6.51 (ddd, 1H, J = 16.8, 11.1, 10.0 Hz), 6.11 (t, 1H, J = 11.1 Hz), 5.67 (t, 1H, J = 10.8 Hz), 5.52-5.18 (m, 7H), 4.94 (t, 1H, J = 6.0 Hz), 4.87-4.47 (m, 9H), 3.94 (br s, 4H), 3.93 (s, 3H), 3.54 (s, 3H), 3.40 (m, 2H), 3.19 (dd, 1H, J = 4.5,

6.9 Hz), 2.87 (m, 2H), 2.72 (m, 2H), 2.32-1.89 (m, 7H), 1.45 (d, 3H, J = 6.6 Hz), 1.15-01.02 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) 174.2, 159.2, 159.0, 156.9, 133.6, 133.5, 133.4, 132.2, 131.3, 130.9, 129.8, 129.6, 129.5, 129.2, 128.7, 127.8, 113.8, 113.7, 95.4, 88.0, 82.7, 79.9, 78.4, 76.5, 75.0, 55.9, 55.7, 55.3, 40.5, 38.6, 37.7, 36.0, 35.4, 34.3, 31.3, 30.6, 23.9, 23.6, 23.5, 19.0, 17.8, 14.4, 12.1, 9.8; LRMS (ESI) 872.4 (M + K).

[00136] Carbamic acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-dihydroxy-14-[(2*S*,3*S*,4*S*,5*R*)-4-hydroxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl ester (40). A solution of the above lactone (2.83 mg, 0.005 mmol) in THF (2 mL) was treated with aqueous 4N HCl (1 mL). The flask was fitted with a glass stopper and the resulting solution was stirred at room temperature for 48 h. Saturated aqueous K_2CO_3 was added dropwise followed by EtOAc. The aqueous layer was extracted with EtOAc and the combined extracts were dried over $MgSO_4$. Filtration and concentration followed by simple short flash column chromatography (EtOAc/hexane/ether 3:2) provided the crude MOM-deprotected compound. A solution of PMB ether in CH_2Cl_2 (2 mL) at 0 °C was treated with $NaHCO_3$ (4.2 mg, 0.5 mmol). After 1 h, the mixture was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2 and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by flash column chromatography (EtOAc/hexane 3:2) provided carbamate **40** (1.1 mg, 0.002 mmol) as a colorless oil: IR ($CHCl_3$) 2995, 2937, 2323, 1755, 1449, 1374, 1242, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 6.63 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.06 (t, 1H, J = 11.0 Hz), 5.46-5.32 (m, 5H), 5.25 (d, 1H, J = 17 Hz), 5.14 (d, 1H, J = 10.0 Hz), 4.94 (t, 1H, J = 6.0 Hz), 4.74 9m, 1H), 4.60 (br s, 1H), 4.54 (m, 1H), 3.65 (m, 1H), 3.38 (d, 1H, J = 5.0 Hz), 3.27 (t, 1H, J = 6.0 Hz), 3.00 (m, 1H), 2.78 (m, 1H), 2.63 (m, 2H), 2.18 (m, 1H), 2.01 (m, 1H), 1.83 (m, 1H), 1.77 (m, 1H), 1. 35 (d, 3H, J = 7.0), 1.01-0.93 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) 174.2, 157.3, 133.6, 132.9, 129.6, 128.9, 125.0, 121.4, 118.0, 95.5, 82.6, 79.7, 79.2, 72.8, 55.9, 40.5, 39.9, 38.6, 35.4, 34.7, 31.6, 23.8, 19.2, 18.2, 17.7, 15.7, 14.8, 12.0; LRMS (ESI) 571.4 (M + Ka); HRMS (ESI) calcd for $C_{31}H_{51}NO_7Na$ 588.3303, found 588.3336 (M + K); $[\alpha]^{20}_D$ +34.0 (*c* 0.05, $CHCl_3$).

[00137] Carbamic acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-dihydroxy-14-[(2*S*,3*S*,4*S*,5*R*)-4-methoxymethoxy-3,5-dimethyl-6-oxotetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl ester (41). Carbamate **39** (8.49 mg, 0.01 mmol) was subjected to the lactonization procedure described above. The removal of the PMB protecting group was accomplished by treating with

$NaHCO_3$ and DDQ. Flash chromatography (EtOAc/hexane 3:2) provided **41** (2.9 mg, 49 % overall 3 steps) as a colorless oil: IR ($CHCl_3$) 3404, 2362, 1749, 1373, 1241, 1049 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.62 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.04 (t, 1H, J = 11.0 Hz), 5.48-5.33 (m, 5H), 5.24 (d, 1H, J = 17 Hz), 5.13 (d, 1H, J = 10.0 Hz), 4.77-4.60 (br m, 5H), 4.48 (m, 1H), 3.65 (m, 1H), 3.41 (s, 3H), 3.28 (d, 1H, J = 7.0 Hz), 3.23 (t, 1H, J = 5.5 Hz), 3.02 (m, 1H), 2.62 (m, 2H), 2.25-2.18 (m, 3H), 2.04 (m, 2H), 1.90 (m, 1H), 1.88 (m, 1H), 1.83 (m, 1H), 1.77-1.67 (m, 2H), 1.51 (m, 2H), 1.34 (d, 3H, J = 7.0), 1.02-0.92 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) 174.1, 157.3, 133.6, 132.9, 132.2, 129.6, 128.9, 125.0, 121.4, 118.0, 95.5, 82.6, 79.7, 79.2, 72.8, 55.9, 40.5, 39.8, 38.6, 35.4, 34.9, 34.7, 31.6, 23.8, 19.2, 18.2, 17.2, 15.7, 14.8, 12.0; LRMS (ESI) 616.3 (M + Na); HRMS (ESI) calcd for $C_{33}H_{55}NO_8Na$ 616.3825, found 616.3829 (M + Na); $[\alpha]^{20}_D$ +59.0 (*c* 0.1, $CHCl_3$).

[00138] Carbamic acid, (1*S*,2*S*,3*R*,6*Z*,8*S*,9*S*,10*S*,11*Z*)-3,9-dihydroxy-14-[(2*S*,3*S*,4*S*,5*R*,6*R*)-6-methoxy-4-methoxymethoxy-3,5-dimethyltetrahydropyran-2-yl]-2,8,10-trimethyl-1-[(1*S*,2*Z*)-1-methylpenta-2,4-dienyl]tetradeca-6,11-dienyl ester (42). Carbamate **39** (4.25 mg, 0.005 mmol) was subjected to the deprotection procedure of PMB described in the preparation of **40**. Flash chromatography (EtOAc/hexane 3:2) of the crude product provided **42** (2.8 mg, 92 %) as a colorless oil: IR ($CHCl_3$) 3115, 2749, 2328, 1676, 1508, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.76 (ddd, 1H, J = 16.8, 11.0, 10.1 Hz), 6.18 (t, 1H, J = 10.8 Hz), 5.70-5.46 (m, 5H), 5.35 (d, 1H, J = 16.8 Hz), 4.49 (dd, J = 4.5, 6.6 Hz), 4.82 (d, 2H, J = 2.4 Hz), 4. 73 (br s, 2H), 4. 43 (d, 1H, J = 5.1 Hz), 4.15, (m, 1H), 3.78 (m, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 3.36 (t, 2H, J = 6.9 Hz), 3.14 (m, 1H), 2.76 (m, 2H), 2.35-2.18 (m, 6H), 2.00-1.60 (m, 7H), 1.22 (d, 3H, J = 7.2 Hz), 1.16-1.12 (m, 12H), 1.07 (d, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) 157.3, 133.7, 133.5, 132.2, 132.0, 130.0, 128.7, 118.0, 109.6, 103.0, 96.5, 82.1, 79.7, 79.1, 72.7, 55.8, 39.9, 39.5, 38.3, 35.5, 35.0, 34.8, 34.6, 30.2, 29.8, 24.3, 18.1, 17.7, 15.7, 15.4, 14.2, 13.2, 8.1; LRMS (ESI) 632.4 (M + Na); HRMS (ESI) calcd for $C_{33}H_{55}NO_8Na$ 632.4138, found 632.4139; $[\alpha]^{20}_D$ +21.6 (*c* 0.25, $CHCl_3$).

[00139] (12*S*,13*S*,14*S*,19*R*,20*R*,21*R*,22*S*)-21-(*tert*-Butyldimethylsilanyloxy)-13,19-bis-(4-methoxybenzyloxy)-12,14,20,22-tetramethylhexacosa-10,15,23,25-tetraen-1-(*tert*-Butyldimethylsilanyl)-ol (45). NaHMDS (1.0 M in THF, 0.45 mL, 0.45 mmol) was slowly added to a solution of the salt **21** (322 mg, 1.1 mmol) in dry THF (0.3 mL) at 0 °C. The resulting red solution was stirred at room temperature for 20 min. The mixture was cooled to –78 °C and a solution of the aldehyde **44** (120 mg, 0.42 mmol) in THF (0.1 mL x 2) was added dropwise. The mixture was stirred for 20 min at –78 °C and then warmed to room

temperature. After 4 h, the mixture was quenched with saturated NH_4Cl (5 mL) and extracted with ethyl ether (3 x 10 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and the residue was column chromatographed (hexane/ether 9:1) to yield 163 mg (75 %) as a colorless oil: IR ($CHCl_3$) 2928, 2854, 1617, 1517, 1462, 1390, 1249, 1114, 1035, 833, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.38 (m, 2H), 6.90-6.85 (m, 2H), 5.42 (s, 1H), 5.39 (ddd, J = 11.7, 10.2, 7.2 Hz, 1H), 5.24 (apparent t, J = 10.2 Hz, 1H), 4.08-4.00 (m, 2H), 3.79 (s, 3H), 3.61 (t, J = 6.5 Hz, 2H), 3.54 (dd, J = 10.5, 1.9 Hz, 1H), 2.69 (dd, J = 16.1, 9.2 Hz, 1H), 2.04 (apparent d, J = 6.6 Hz, 2H), 1.71-1.68 (m, 1H), 1.54-1.50 (m, 3H), 1.27 (br, 1H), 1.20 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 133.3, 132.6, 132.5, 132.1, 130.7, 128.9, 128.7, 127.6, 113.7, 101.8, 83.9, 74.2, 63.6, 55.5, 33.9, 33.3, 30.4, 30.1, 30.0, 29.9, 29.8, 29.7, 28.0, 26.3, 26.2, 18.7, 16.3, 11.5, –4.9; LRMS (API-ES) 541$(M+Na)^+$, 493, 431, 365, 295, 251; $[\alpha]^{20}_D$ +26.0 (*c* 0.90, $CHCl_3$).

[00140] To a solution of 164 mg (0.32 mmol) of the above acetal in dry CH_2Cl_2 (2.0 mL) DIBAL (1.0 M in hexane, 0.95 mL, 0.96 mmol) at 0 °C was added dropwise. After 2 h, the mixture was quenched with saturated sodium potassium tartrate solution (20 mL) followed by vigorously stirring for 4 h. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, flash column chromatography (hexane/ether 9:1) provided 115 mg (70 %) of alcohol as a colorless oil: IR ($CHCl_3$) 3430, 2928, 2855, 1613, 1514, 1463, 1249, 1098, 1038, 835, 776 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 6.88-6.85 (m, 2H), 4.59 (d, J = 10.8 Hz, 1H), 4.47 (d, J = 10.8 Hz, 1H), 3.80 (s, 3H), 3.65-3.50 (m, 4H), 3.36 (dd, J = 5.9, 3.9 Hz, 1H), 2.86-2.78 (m, 1H), 2.11-2.01 (m, 2H), 1.98-1.95 (m, 1H), 1.77 (br, 1H), 1.50 (br, 3H), 1.27 (br, 1H), 0.97 (apparent t, J = 7.1 Hz, 6H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 132.8, 131.1, 130.0, 129.5, 113.8, 84.5, 73.7, 66.4, 63.5, 55.3, 37.6, 34.6, 33.0, 29.8, 29.7, 29.64, 29.61, 29.5, 27.7, 26.1, 25.9, 18.8, 18.4, 11.7, –5.1; LRMS (EI) 541 $(M+Na)^+$, 462, 375, 325, 255, 207, 122; HRMS (EI) calcd for $C_{27}H_{47}O_4Si_1$ 463.3254 $(M-^tBu)^+$, found 463.3254; $[\alpha]^{20}_D$ +25.9 (*c* 0.48, $CHCl_3$).

[00141] The above alcohol (94 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) was treated with Dess-Martin periodinane (120 mg, 0.27 mmol). After 2 h, the mixture was quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with ethyl ether (10 mL x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration

followed by short flash column chromatography (hexane/EtOAc 9:1) to remove the residue from Dess-Martin reagent provided 78 mg (83%) of the crude aldehyde as a colorless oil which was used for the next reaction without further purification. NaHMDS (1.0 M in THF, 0.15 mL, 0.15 mmol) was slowly added to a solution of the salt **33** (140 mg, 0.17 mmol) in dry THF (0.15 mL) at 0 °C. The resulting red solution was stirred at room temperature for 20 min. The mixture was cooled to –78 °C and a solution of the aldehyde above (69 mg, 0.13 mmol) in THF (0.05 mL x 2) was added dropwise. The mixture was stirred for 20 min at –78 °C and then warmed to room temperature. After 4 h at room temperature, the mixture was quenched with saturated NH_4Cl (2 mL) and extracted with ethyl ether (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and the residue was purified by column chromatography (hexane/ether 9:1) to yield **45** (111 mg, 65 % for 2 steps) as a colorless oil: IR ($CHCl_3$) 2926, 1612, 1513, 1462, 1361, 1250, 1173, 1098, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.33 (m, 4H), 6.99-6.93 (m, 4H), 6.49 (ddd, J = 16.8, 10.8, 10.7 Hz, 1H), 6.06 (apparent t, J = 11.0 Hz, 1H), 5.59 (d, J = 10.5 Hz, 1H), 5.51 (d, J = 9.8 Hz, 1H), 5.44-5.31 (m, 3H), 5.23 (d, J = 16.8 Hz, 1H), 5.13 (d, J = 10.1 Hz, 1H), 4.68-4.57 (m, 3H), 4.42 (d, J = 11.3 Hz, 1H), 3.90 (s, 6H), 3.69 (t, J = 6.5 Hz, 2H), 3.37-3.36 (m, 1H), 3.14 (q, J = 3.7 Hz, 1H), 2.82-2.71 (m, 2H), 2.08-2.00 (m, 4H), 1.78-1.77 (m, 2H), 1.71-1.58 (m, 6H), 1.36 (br, 11H), 1.11 (d, J = 6.7 Hz, 6H), 1.04-1.00 (m, 24H), 0.15 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 159.1, 134.8, 133.8, 132.5, 132.0, 131.5, 131.1, 129.9, 129.7, 129.2, 129.1, 128.6, 117.3, 113.8, 113.7, 88.1, 79.1, 74.8, 71.0, 63.4, 55.4, 40.1, 36.6, 35.8, 35.3, 33.0, 31.5, 30.0, 29.8, 29.7, 29.6, 27.7, 26.4, 26.1, 23.8, 19.0, 18.9, 18.5, 17.6, 11.1, –3.2, –3.3, –5.1; LRMS (EI) 890($M-^tBu$)$^+$, 866 ; HRMS (EI) calcd for $C_{54}H_{89}O_6Si_2$ 865.5258($M-^tBu$)$^+$, found 865.5225; $[\alpha]^{20}_D$ +20.5 (*c* 0.60, $CHCl_3$).

[00142] (12*S*,13*S*,14*S*,19*R*,20*R*,21*R*,22*S*)-21-(*tert*-Butyldimethylsilanyloxy)-13,19-bis-(4-methoxybenzyloxy)-12,14,20,22-tetramethylhexacosa-10,15,23,25-tetraenoic acid (46). To a solution of TBS ether **45** (93 mg, 0.098 mmol) in THF (2 ml) was slowly added HF-pyridine in pyridine (4 ml, prepared by slow addition of 1.2 ml pyridine to 0.3 ml HF-pyridine complex followed by dilution with 3 ml THF). The mixture was stirred overnight at room temperature and quenched with sat'd $NaHCO_3$ (20 ml). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layer was washed with sat'd $CuSO_4$ (3 x 20 ml), dried over $MgSO_4$, and concentrated. Flash column chromatography (EtOAc/Hexane 1:4) afforded 64 mg (78%) of the alcohol: IR ($CHCl_3$) 3429, 2928, 2855, 1694, 1612, 1513, 1462, 1250, 1173, 1038, 836, 773 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$) δ 7.40-7.33 (m, 4H), 6.99-6.95 (m, 4H), 6.49 (ddd, *J* = 16.8, 10.6, 10.5 Hz, 1H), 6.05 (apparent t, *J* = 11.0 Hz, 1H), 5.58 (d, *J* = 10.9 Hz, 1H), 5.52 (d, *J* = 9.7 Hz, 1H), 5.46-5.34 (m, 2H), 5.23 (d, *J* = 16.8 Hz, 1H), 5.14 (d, *J* = 10.1 Hz, 1H), 4.68-4.57 (m, 3H), 4.45-4.41 (m, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.72-3.67 (m, 2H), 3.37-3.36 (m, 2H), 3.14 (q, *J* = 3.6 Hz, 1H), 2.80-2.70 (m, 2H), 2.08-1.99 (m,4H), 1.78-1.77 (m, 2H), 1.71-1.58 (m, 6H), 1.36 (br, 11H), 1.10 (d, *J* = 6.6 Hz, 6H), 1.02 (d, *J* = 2.6 Hz, 6H), 1.00 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 159.1, 134.8, 134.8, 133.8, 132.5, 132.1, 131.5, 131.1, 129.9, 129.7, 129.2, 129.1, 128.6, 117.3, 113.8, 113.7, 88.1, 79.0, 76.7, 74.8, 71.0, 63.1, 55.4, 40.1, 36.6, 35.8, 35.4, 32.9, 31.4, 30.0, 29.7, 29.63, 29.56, 27.6, 26.4, 25.9, 23.8, 19.0, 18.9, 18.6, 17.6, 11.1, –3.2, –3.3; LRMS (API-ES) 871 $(M+K)^+$, 445, 364, 338; $[\alpha]^{20}_D$ +27.0 (*c* 0.24, $CHCl_3$).

[00143] The above alcohol (0.213 g, 0.26 mmol) in CH_2Cl_2 (10 mL) was treated with Dess-Martin periodinane (160 mg, 0.38 mmol). After 2 h, the mixture was quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with ethyl ether (10 mL x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography (hexane/EtOAc 8:2) to remove the residue from Dess-Martin reagent provided the aldehyde as a colorless oil which was used for the next reaction without further purification. A solution of the above aldehyde in 1 ml of THF and 0.5 ml of H_2O was treated with 0.74 ml (1.48 mmol) of a 2M solution of 2-methyl-2-butene in THF, 0.11 g (0.77 mmol) of $NaH_2PO_4 \cdot H_2O$ and 0.087 g (0.77 mmol) of $NaClO_2$. The reaction mixture was stirred for 2 h, diluted with 20 ml of 1N HCl and extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and the residue was chromatographed on SiO_2 (EtOAc/hexane 1:3) to yield 192 mg (89 % for 2 steps) of the acid **46** as a viscous oil: IR ($CHCl_3$) 3398, 2929, 2855, 1710, 1612, 1513, 1249, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.40 (m, 4H), 7.05-6.99 (m, 4H), 6.55 (ddd, *J* = 16.8, 10.6, 10.3 Hz, 1H), 6.12 (apparent t, *J* = 11.0 Hz, 1H), 5.66 (d; *J* = 10.6 Hz, 1H), 5.58 (d, *J* = 11.0 Hz, 1H), 5.52-5.37 (m, 3H), 5.30 (d, *J* = 16.8 Hz, 1H), 5.21 (d, *J* = 10.0 Hz, 1H), 4.74-4.64 (m, 3H), 4.52-4.48 (m, 1H), 3.95 (s, 6H), 3.72 (dd, *J* = 6.2, 3.3 Hz, 1H), 3.43 (dd, *J* = 10.5, 5.9 Hz, 1H), 3.21 (q, *J* = 3.8 Hz, 1H), 2.87-2.77 (m, 3H), 2.49 (t, *J* = 7.4 Hz, 2H), 2.15-2.09 (m, 4H), 1.87-1.70 (m, 5H), 1.43 (br, 11H), 1.17 (d, *J* = 6.8 Hz, 6H), 1.10 (d, *J* = 3.0 Hz, 6H), 1.07 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.06 159.3, 159.1, 134.8, 133.8, 132.5, 132.1, 131.5, 131.1, 129.8, 129.7, 129.2, 129.1, 128.6, 117.3, 113.8, 113.7, 88.1, 79.0, 76.7, 74.8, 70.9, 55.4, 40.1, 36.6, 35.8, 35.4, 34.2, 31.4, 29.9,

29.5, 29.3, 29.2, 27.6, 26.4, 24.8, 23.8, 19.0, 18.9, 18.6, 17.6, 11.1, –3.2, –3.3; LRMS (API-ES) 846 $(M)^-$, 845 $(M-H)^-$; $[\alpha]^{20}_D$ +24.5 (*c* 0.38, $CHCl_3$).

[00144] **(1*S*,13*S*,14*S*,15*S*,20*R*,21*R*,22*R*)-14,20-Dihydroxy-13,15,21-trimethyl-22-(1-methylpenta-2,4-dienyl)-oxacyclodocosa-11,16-dien-2-one (43).** To **46** (146 mg, 0.17 mmol) in THF (2 mL) was added TBAF (1.0 M in THF, 1.72 mL, 1.72 mmol) and the mixture was stirred at room temperature for 48 h. The reaction mixture was diluted with ethyl ether (30 mL) and was washed with water (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, the crude was chromatographed on SiO_2 (EtOAc/hexane 1:4) to yield 72 mg (57%) of the acid as a colorless oil: IR ($CHCl_3$) 3467, 2927, 2854, 1710, 1612, 1513, 1460, 1248, 1174, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.32 (m, 4H), 6.98-6.93 (m, 4H), 6.69 (ddd, *J* = 16.7, 10.7, 10.6 Hz, 1H), 6.18 (apparent t, *J* = 10.9 Hz, 1H), 5.57 (d, *J* = 10.4 Hz, 1H), 5.50 (d, *J* = 10.9 Hz, 1H), 5.46-5.37 (m, 3H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.1 Hz, 1H), 4.69-4.58 (m, 3H), 4.47-4.44 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.58-3.56 (m, 2H), 3.16 (q, *J* = 3.5 Hz, 1H), 2.86-2.79 (m, 2H), 2.73-2.70 (m, 1H), 2.42 (t, *J* = 7.3 Hz, 2H), 2.14-2.02 (m, 4H), 1.91-1.89 (m, 1H), 1.81-1.71 (m, 4H), 1.37 (br, 11H), 1.12 (d, *J* = 6.6 Hz, 6H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6 159.3, 159.1, 135.6, 134.1, 132.4, 132.0, 131.4, 130.4, 130.1, 129.9, 129.6, 129.3, 128.3, 117.9, 113.9, 113.8, 88.1, 83.0, 78.2, 74.9, 71.0, 55.4, 36.7, 36.2, 36.1, 35.4, 34.1, 30.6, 29.9, 29.8, 29.5, 29.3, 29.2, 27.6, 24.8, 23.7, 19.0, 17.7, 17.5, 6.9; LRMS (API-ES) 755.5 $(M+Na)^+$, 866; $[\alpha]^{20}_D$ +31.3 (*c* 0.64, $CHCl_3$).

[00145] A solution of above hydroxy acid (60 mg, 0.081 mmol) in THF (1 ml) was treated at 0 °C with Et_3N (0.068 ml, 0.49 mmol) and 2,4,6-trichlorobenzoyl chloride (0.064 ml, 0.41 mmol). The reaction mixture was stirred at 0 °C for 30 min and then added to a 4-DMAP (41 ml, 0.81 mmol, 0.02 M solution in toluene) at 25 °C and stirred for overnight. The reaction mixture was concentrated, EtOAc (10 mL) was added and the crude was washed with 1N HCl (2 x 10 ml), dried over $MgSO_4$. Purification by flash column chromatography (EtOAc/hexane 1:9) furnished macrolactone (33 mg, 57%) as a colorless oil: IR ($CHCl_3$) 2926, 2855, 1730, 1612, 1513, 1459, 1248, 1174, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.35 (m, 4H), 6.98-6.94 (m, 4H), 6.55 (ddd, *J* = 16.5, 10.9, 10.6 Hz, 1H), 6.06 (apparent t, *J* = 10.8 Hz, 1H), 5.66 (apparent t, *J* = 10.0 Hz, 1H), 5.48-5.29 (m, 4H), 5.24 (d, *J* = 6.9 Hz, 1H), 5.16 (d, *J* = 10.3 Hz, 1H), 5.01 (dd, *J* = 7.5, 3.5 Hz, 1H), 4.66-4.53 (m, 3H), 4.43 (d, *J* = 10.6 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.20-3.18 (m, 1H), 3.13 (d, *J* = 9.6 Hz, 1H), 2.97-2.89 (m, 1H), 2.76-2.64 (m, 2H), 2.37-2.19 (m, 3H), 2.04-1.98 (m, 4H), 1.78-1.57 (m, 4H),

1.38 (br, 11H), 1.16-1.10 (m, 9H), 0.99 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4 159.6, 159.3, 134.4, 133.7, 132.5, 131.8, 131.4, 131.0, 130.2, 130.0, 129.9, 129.4, 129.3, 118.0, 114.2, 114.0, 89.0, 80.6, 76.6, 75.7, 72.0, 55.6, 38.3, 37.5, 36.1, 34.9, 34.7, 31.7, 30.0, 29.6, 29.0, 28.8, 28.7, 27.2, 25.1, 24.5, 20.0, 18.8, 17.4, 10.4; HRMS (EI) calcd for $C_{46}H_{66}O_6$ 714.4859, found 714.4848; $[\alpha]^{20}_D$ +5.8 (*c* 0.39, $CHCl_3$).

[00146] The above macrolactone (12 mg, 16. μmol) was dissolved in CH_2Cl_2 (2 ml) - H_2O (0.2 ml) and DDQ (12 mg, 53 μmol) was added at 0 °C. After 1 h of stirring at 0 °C, the reaction mixture was quenched by adding sat'd $NaHCO_3$ (5 ml). The organic phase was washed by sat'd $NaHCO_3$ solution (3 x 20 ml) and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (EtOAc/hexane 1:4) furnished macrolactone (6.8 mg, 85%) as a colorless oil: IR ($CHCl_3$) 3434, 2926, 2854, 2359, 2341, 1731, 1651, 1505, 1456, 1377, 1261, 1107, 965, 905, 803 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (dt, J = 16.8, 10.9 Hz, 1H), 6.13 (t, J = 10.9 Hz, 1H), 5.60-5.56(m, 1H), 5.54-5.46 (m, 2H), 5.42-5.30 (m, 3H), 5.25 (d, J = 10.1 Hz, 1H), 5.08 (dd, J = 8.9, 2.6 Hz, 1H), 3.49 (ddd, J = 9.5, 7.4, 2.8 Hz, 1H), 3.37 (dd, J = 7.3, 4.3 Hz, 1H), 3.18-3.05 (m, 1H), 2.86-2.74 (m, 2H), 2.43-2.30 (m, 3H), 2.23-2.05 (m, 2H), 1.84 (br, 9H), 1.42 (br, 9H), 1.23 (d, J = 6.8 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 134.6, 132.4, 131.9, 130.5, 129.9, 129.8, 129.1, 117.9, 80.1, 76.4, 72.9, 40.0, 36.9, 35.4, 34.8, 34.6, 34.5, 29.0, 28.6, 28.4, 28.3, 28.1, 26.9, 24.8, 24.2, 18.9, 18.8, 17.1, 9.6; HRMS (EI) calcd for $C_{30}H_{49}O_3$ 456.3603 $(M\text{-}OH)^+$, found 456.3622; $[\alpha]^{20}_D$ +29.0 (*c* 0.10, $CHCl_3$).

[00147] (12*S*,13*S*,14*S*,19*R*,20*R*,21*R*,22*S*)-12,14,20,22-Tetramethylhexacosa-10,15,23,25-tetraene-1,13,19,21-tetraol (47). The protected alcohol **45** (54 mg, 57 μmol) was dissolved in CH_2Cl_2 (3 ml) - H_2O (0.3ml) and DDQ (39 mg, 0.17 mmol) was added at 0 °C. After 1 h of stirring at 0 °C, the reaction mixture was quenched by adding sat'd $NaHCO_3$ (10 ml). The organic phase was washed by sat'd $NaHCO_3$ solution (3 x 20 ml) and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (EtOAc/hexane 1:9) furnished the diol (20 mg, 53%) as a colorless oil: IR ($CHCl_3$) 3434, 2958, 2924, 2853, 2362, 1463, 1382, 1246, 1095, 1021, 832, 773 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (ddd, J = 16.7, 10.7, 10.6 Hz, 1H), 6.05 (apparent t, J = 11.0 Hz, 1H), 5.62 (t, J = 10.3 Hz, 1H), 5.55-5.45 (m, 1H), 5.41-5.27 (m, 3H), 5.21 (d, J = 7.6 Hz, 1H), 5.14 (d, J = 10.2 Hz, 1H), 3.74-3.72 (m, 1H), 3.65-3.63 (m, 1H), 3.60 (t, J = 6.6 Hz, 2H), 3.20 (dd, J = 6.1, 5.4 Hz, 1H), 2.96-2.91 (m, 1H), 2.69-2.56 (m, 2H), 2.17-1.95 (m, 4H), 1.60-1.51 (m,

8H), 1.27 (br, 11H), 1.03 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.92 (s, 11H), 0.90 (s, 10H), 0.10 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H); LRMS (API-ES) 729.5 $(M+Na)^+$, 557.5, 413, 243; $[\alpha]^{20}_D$ +48.0 (*c* 0.025, $CHCl_3$).

[00148] To an above solution (20 mg, 28 μmol) in THF (1 mL) was added TBAF (1.0 M in THF, 0.28 mL, 0.28 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc (10 mL) and was washed with water (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, the crude was chromatographed on SiO_2 (EtOAc/hexane 1:3) to yield 11 mg (83%) of the alcohol **47** as a colorless oil: IR ($CHCl_3$) 3378, 2925, 2853, 2359, 1651, 1455, 1377, 1056, 971, 903 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) δ□□□. ddd, J = 16.8, 10.6, 10.5 Hz, 1H), 6.21 (apparent t, J = 11.0 Hz, 1H), 5.54-5.46 (m, 1H), 5.43-5.36 (m, 2H), 5.31-5.18 (m, 4H), 3.84 (dd, J = 7.3, 4.6 Hz, 1H), 3.65 (apparent t, J = 6.6 Hz, 2H), 3.46 (d, J = 9.3 Hz, 1H), 3.22 (t, J = 5.6 Hz, 1H), 2.86-2.78 (m, 1H), 2.72-2.59 (m, 2H), 2.23-2.02 (m, 4H), 1.71-1.53 (m, 8H), 1.29-1.26 (m, 13H), 1.01-0.91 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 133.8, 132.2, 132.1, 131.9, 131.3, 128.9, 119.1, 80.6, 79.1, 76.1, 63.2, 53.6, 37.6, 36.4, 35.5, 35.1, 34.5, 32.9, 29.8, 29.6, 29.5, 29.4, 27.7, 25.8, 24.2, 18.1, 16.7, 15.3, 4.5; LRMS (API-ES) 517 $(M+K)^+$, 501 $(M+Na)^+$, 479 $(M+H)^+$, 461 $(M+H-H_2O)^+$, 443; $[\alpha]^{20}_D$ +43.3 (*c* 0.18, $CHCl_3$).

[00149] (12*S*,13*S*,14*S*,19*R*,20*R*,21*R*,22*S*)-13,19,21-Trihydroxy-12,14,20,22-tetramethylhexacosa-10,15,23,25-tetraenoic acid methyl ester (48). To an acid **46** (34 mg, 40 μmol) in DMF (3 ml) K_2CO_3 (0.017g, 0.12 mmol) and MeI (0.009ml, 0.06mmol) were added and stirred for 1h at room temperature. The reaction mixture was quenched by H_2O (1 ml) and extracted with EtOAc (3 x 5 ml) and washed with brine (5 ml). The organic phase was dried over $MgSO_4$ and evaporated and the residue was used as crude without no further purification (36 mg, 85%): IR ($CHCl_3$) 2928, 2855, 1740, 1613, 1513, 1462, 1301, 1248, 1172, 1038, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.24 (m, 4H), 6.90-6.86 (m, 4H), 6.39 (ddd, J = 16.9, 10.7, 10.6 Hz, 1H), 5.96 (apparent t, J = 11.0 Hz, 1H), 5.50 (d, J = 10.3 Hz, 1H), 5.42 (d, J = 10.7 Hz, 1H), 5.36-5.21 (m, 3H), 5.14 (d, J = 16.8 Hz, 1H), 5.04 (d, J = 9.9 Hz, 1H), 4.59-4.47 (m, 3H), 4.39-4.31 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.67 (s, 3H), 3.57 (dd, J = 5.9, 3.3 Hz, 1H), 3.28-3.26 (m, , 1H), 3.05 (q, J = 3.7 Hz, 1H), 2.71-2.61 (m, 3H), 2.30 (t, J = 7.5 Hz, 2H), 1.99-1.90 (m, 4H), 1.68-1.59 (m, 5H), 1.26 (br, 11H), 1.01 (d, J = 6.6 Hz, 6H), 0.91 (br, 15H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 159.3, 159.1, 134.8, 133.8, 132.5, 132.1, 131.5, 131.1, 129.8, 129.7, 129.2, 129.1, 128.6, 117.3, 113.8, 113.7, 88.1, 79.0, 55.4, 51.6, 40.0, 36.5, 35.8, 35.4, 34.2, 31.4, 29.9, 29.8, 29.5, 29.4,

29.3, 27.6, 26.4, 25.1, 23.7, 19.0, 18.6, 17.6, 11.1, –3.2, –3.3; LRMS (API-ES) 883.6 $(M+Na)^+$; $[\alpha]^{20}_D$ +24.7 (*c* 1.6, $CHCl_3$).

[00150] The above ester (41 mg, 47 μmol) was dissolved in CH_2Cl_2 (2 ml) - H_2O (0.4 ml) and DDQ (32 mg, 0.14 mmol) was added at 0 °C and was followed same procedure for **43**. Purification by flash column chromatography (EtOAc/Hexane 1:8) furnished the diol (25 mg, 84%) as a colorless oil: IR ($CHCl_3$) 3487, 2924, 2850, 1741, 1602, 1463, 1367, 1249, 838, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.59 (ddd, *J* = 16.8, 10.8, 10.6 Hz, 1H), 6.04 (apparent t, *J* = 11.0 Hz, 1H), 5.62 (t, *J* = 10.1 Hz, 1H), 5.54-5.46 (m, 1H), 5.41-5.30 (m, 3H), 5.23 (d, *J* = 17.9 Hz, 1H), 5.14 (d, *J* = 10.2 Hz, 1H), 3.75-3.71 (m, 1H), 3.68 (s, 3H), 3.65-3.63 (m, 1H), 3.20 (t, *J* = 5.8 Hz, 1H), 2.96-2.90 (m, 1H), 2.69-2.58 (m, 2H), 2.31 (t, *J* = 7.6 Hz, 2H), 2.17-1.95 (m, 5H), 1.62-1.52 (m, 5H), 1.29 (br, 11H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.93 (s, 12H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 134.4, 133.7, 132.0, 131.4, 129.4, 128.8, 118.1, 114.3, 79.0, 78.7, 71.2, 51.4, 42.5, 35.8, 35.7, 35.5, 34.4, 34.1, 29.7, 29.3, 29.2, 29.1, 27.6, 26.1, 24.9, 24.3, 19.2, 18.3, 17.9, 15.0, 14.1, 9.5, –3.7, –3.9; LRMS (API-ES) 643.5 $(M+Na)^+$, 471.4; $[\alpha]^{20}_D$ +41.6 (*c* 0.74, $CHCl_3$).

[00151] To an above solution (25 mg, 40 μmol) in THF (2 mL) was added TBAF (1.0 M in THF, 0.12 mL, 0.12 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc (10 mL) and was washed with water (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, the crude was chromatographed on SiO_2 (EtOAc/hexane 1:3) to yield 8.5 mg (93%) of the ester **48** as a colorless oil: IR ($CHCl_3$) 3444, 2952, 2925, 2847, 1734, 1451, 1379, 1237, 1197, 1451, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ□□□. ddd, *J* = 16.8, 10.7, 10.6 Hz, 1H), 6.20 (apparent t, *J* = 10.7 Hz, 1H), 5.54-5.46 (m, 1H), 5.43-5.36 (m, 2H), 5.31-5.18 (m, 4H), 3.83 (dd, *J* = 9.0, 3.9 Hz, 1H), 3.67 (s, 3H), 3.46 (dd, *J* = 9.3, 2.0 Hz, 1H), 3.22 (apparent t, *J* = 5.4 Hz, 1H), 2.85-2.78 (m, 1H), 2.72-2.59 (m, 2H), 2.31 (t, *J* = 7.4 Hz, 3H), 2.20-1.95 (m, 3H), 1.74-1.59 (m, 6H), 1.29 (br, 12H), 1.01-0.93 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 134.4, 133.7, 131.9, 131.3, 128.7, 118.9, 80.5, 79.1, 76.0, 51.4, 37.7, 36.4, 35.5, 35.1, 34.5, 34.1, 30.0, 29.3, 29.2, 29.1, 27.6, 24.9, 24.2, 22.7, 17.9, 16.7, 15.1, 4.5; LRMS (API-ES) 529 $(M+Na)^+$, 507, 489, 471, 453; $[\alpha]^{20}_D$ +27.3 (*c* 0.43, $CHCl_3$).

[00152] **(12*S*,13*S*,14*S*,19*R*,20*R*,21*R*,22*S*)-13,19,21-Trihydroxy-12,14,20,22-tetramethylhexacosa-10,15,23,25-tetraenoic acid (49).** To an above solution **48** (8.0 mg) in THF-H_2O (0.3 ml, 0.1 ml each) was added $LiOH{\cdot}H_2O$ (1.3 mg) and the solution was warmed

to 60 °C. After stirring 6 h, 1N HCl (1 ml) was added and reaction mixture was extracted with CH_2Cl_2 (10 ml x 2). After drying over $MgSO_4$ and evaporation under vacuum, the crude was chromatographed on SiO_2 (EtOAc/hexane 1:3) to yield 6.3 mg (81%) of the **49** as a colorless oil: IR ($CHCl_3$) 3412, 2964, 2921, 2850, 2658, 1710, 1459, 1404, 1268, 971, 903 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.64 (ddd, *J* = 16.7, 10.6, 10.0 Hz, 1H), 6.20 (apparent t, *J* = 10.9 Hz, 1H), 5.54-5.46 (m, 1H), 5.42-5.36 (m, 2H), 5.32-5.18 (m, 4H), 3.88-3.84 (m, 1H), 3.48 (d, *J* = 9.2 Hz, 1H), 3.23 (apparent t, *J* = 5.7 Hz, 1H), 2.86-2.76 (m, 1H), 2.69-2.60 (m, 2H), 2.34 (t, *J* = 7.4 Hz, 2H), 2.21-2.04 (m, 5H), 1.70-1.62 (m, 5H), 1.28 (br, 13H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 134.4, 133.8, 132.1, 132.0, 132.0, 131.3, 128.8, 119.1, 80.7, 79.2, 76.2, 37.6, 35.5, 34.6, 29.8, 29.7, 29.5, 29.2, 29.1, 29.0, 27.6, 24.8, 24.2, 22.8, 18.1, 16.7, 15.4, 14.2, 4.5; LRMS (API-ES) 515.3 $(M+Na)^+$, 493 $(M+H)^+$, 475 $(M+H-H_2O)^+$, 457 $(M+H-2H_2O)^+$, 242; $[\alpha]^{20}_D$ +33.0 (*c* 0.23, $CHCl_3$).

[00153] (4*R*,5*R*)-5-(4-Methoxybenzyloxy)-4-methyl-8-oxooct-2-enoic acid ethyl ester (51). To a cooled (0 °C) stirred suspension of NaH (2.27g, 11.3 mmol, 60% dispersion in mineral oil) in THF (130 ml) was added dropwise a solution of triethyl phosphonoacetate (2.27 ml, 11.4 mmol) over 10 min period. The mixture was brought to room temperature with a water bath (30 min) and then cooled back to 0 °C and the aldehyde from **50** (3.43 g, 9.0 mmol) in THF (10 ml) was added. The resulting mixture was stirred for 1 h at 0 °C then pH7 phosphate buffer solution (30 ml) and diethyl ether (100 ml) were added. The mixture was allowed to warm to room temperature and the phase was separated. The organic phase was washed with sat'd NH_4Cl solution (30 ml) and brine (30 ml), dried with $MgSO_4$, filtered and concentrated to give oily crude product. Purification by flash chromatography (EtOAc/hexane 1:4) afforded pure ester (3.82 g, 94%): IR ($CHCl_3$) 2954, 2928, 2855, 1720, 1513, 1250, 1034, 835cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ□□9-7.25 m, 2H), 7.00 (dd, *J* = 15.7, 7.5 Hz, 1H), 6.91-6.84 (m, 2H), 5.83 (d, *J* = 15.7 Hz, 1H), 4.47 (dd, *J* = 14.6, 11.1 Hz, 2H), 4.19 (q, *J* = 7.1Hz, 2H), 3.81 (s, 3H), 3.64-3.52 (m, 2H), 3.37-3.33 (m, 1H), 2.64 (dd, *J* = 13.2, 6.5 Hz, 1H), 1.42-1.68 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 159.3, 151.2, 130.8, 130.4, 129.5, 121.3, 113.9, 81.8, 71.6, 63.1, 60.3, 55.3, 39.8, 28.9, 27.7, 26.1, 18.5, 15.1, 14.4, –5.1; LRMS(API-ES) 489.1 $(M+K)^+$, 435, 263, 204; $[\alpha]^{20}_D$ +6.4 (*c* 0.43, $CHCl_3$).

[00154] To a solution of above TBS ether (0.324 g, 0.72 mmol) in THF (5 ml) was slowly added HF-pyridine in pyridine (8 ml, prepared by slow addition of 2.4 ml pyridine to

0.6 ml HF-pyridine complex followed by dilution with 5 ml THF). The mixture was stirred overnight at room temperature and quenched with sat'd $NaHCO_3$ (20 ml). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layer was washed with sat'd $CuSO_4$ (3 x 20 ml), dried over $MgSO_4$, and concentrated. Flash column chromatography (EtOAc/hexane 1:3) afforded 0.203 g (84%) of the alcohol: IR ($CHCl_3$) 1715, 1612, 1514, 1249, 1180, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7-7.24 m, 2H), 6.98 (dd, J = 15.8, 7.5 Hz, 1H), 6.88-6.85 (m, 2H), 5.83 (d, J = 15.8 Hz, 1H), 4.47 (dd, J = 14.6, 11.1 Hz, 2H), 4.17 (q, J = 7.1Hz, 2H), 3.79 (s, 3H), 3.59-3.56 (m, 2H), 3.37-3.33 (m, 1H), 2.71-2.65 (m, 1H), 2.15 (br, 1H), 1.77-1.40 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 159.3, 150.8, 130.4, 129.6, 121.4, 113.9, 81.9, 71.7, 62.8, 60.4, 55.3, 39.5, 28.9, 27.8, 15.2, 14.4; LRMS(API-ES) 375.1 $(M+K)^+$, 359.1 $(M+Na)^+$, 241, 225; $[\alpha]^{20}_D$ +12.0 (*c* 0.15, $CHCl_3$).

[00155] The above alcohol (0.203 g, 0.61 mmol) in CH_2Cl_2 (6 mL) was treated with Dess-Martin periodinane (0.38 g, 0.90 mmol). After 2 h, the mixture was quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with ethyl ether (10 mL x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography (hexane/EtOAc 3:1) to remove the residue from Dess-Martin reagent provided 0.146 g (72%) of the crude aldehyde **51** as a colorless oil which was used for the next reaction without further purification: ^1H NMR (300 MHz, $CDCl_3$) δ 9.68 (s, 1H), 7.27-7.21 (m, 2H), 6.99 (dd, J = 15.8, 7.3 Hz, 1H), 6.88-6.85 (m, 2H), 5.84 (d, J = 15.8 Hz, 1H), 4.48 (d, J = 11.0 Hz, 1H), 4.34 (d, J = 11.0 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.41-3.31 (m, 1H), 2.73-2.63 (m, 1H), 2.55-2.40 (m, 1H), 1.90-1.78 (m, 1H), 1.71-1.61 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.27-1.22 (m, 2H), 1.10 (d, J = 6.8 Hz, 3H).

[00156] **(4*R*,5*R*,10*S*,11*S*,12*S*,17*R*,18*R*,19*R*,20*S*)-19-(*tert*-Butyldimethylsilanyloxy)-5,11,17-tris-(4-methoxybenzyloxy)-4,10,12,18,20-pentamethyltetracosa-2,8,13,21,23-pentaenoic acid ethyl ester (52).** NaHMDS (1.0 M in THF, 0.49 mL, 0.49 mmol) was slowly added to a solution of the salt **21** (0.35 g, 0.55 mmol) in dry THF (0.50 mL) at 0 °C. The resulting red solution was stirred at room temperature for 20 min. The mixture was cooled to –78 °C and a solution of the aldehyde **51** (146 mg, 0.44 mmol) in THF (0.1 mL) was added dropwise. The mixture was stirred for 20 min at –78 °C and then warmed to room temperature. After 4 h at room temperature, the mixture was quenched with saturated NH_4Cl (2 mL) and extracted with ethyl ether (3 x 10 mL). The combined organic layers were dried

over anhydrous $MgSO_4$, evaporated and the residue was flash column chromatographed (hexane/EtOAc 9:1) to yield (183 mg, 74 %) as a colorless oil: IR ($CHCl_3$) 2962, 2850, 1716, 1614, 1515, 1249, 1179, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.49 m, 2H), 7.41-7.36 (m, 2H), 7.12 (dd, J = 15.8, 7.5 Hz, 1H), 7.00-6.97 (m, 4H), 5.95 (d, J = 15.8 Hz, 1H), 5.56 (s, 1H), 5.52-5.39 (m, 2H), 4.53 (d, J = 3.0 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 4.22-4.14 (m, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.69 (dd, J = 9.6, 1.9 Hz, 1H), 3.46-3.40 (m, 1H), 2.88-2.80 (m, 1H), 2.75-2.67 (m, 1H), 2.36-2.14 (m, 2H), 1.84-1.81 (m, 1H), 1.67-1.55 (m, 2H), 1.43 (t, J = 7.1 Hz, 3H), 1.32 (d, J = 6.9 Hz, 3H), 1.15 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 159.8, 159.3, 151.3, 134.0, 131.8, 130.9, 129.7, 129.5, 127.4, 121.1, 113.9, 113.5, 101.7, 83.9, 81.5, 74.0, 71.7, 60.3, 55.4, 39.7, 33.8, 31.5, 30.1, 23.9, 16.1, 15.0, 14.4, 11.2; LRMS (API-ES) 605.3 $(M+K)^+$, 589.3 $(M+Na)^+$, 567.3 $(M+H)^+$; $[\alpha]^{20}_D$ +30.0 (*c* 0.01, $CHCl_3$).

[00157] Trimethylsilyl chloride (0.24 ml, 1.9 mmol) was added dropwise to a stirred mixture containing above acetal (0.177 g, 0.31 mmol), $NaCNBH_3$ (0.12 g, 1.9 mmol) and 4A molecular sieve in acetonitrile (6 ml) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and filtered through Celite, poured into 1N HCl (10 ml). The aqueous phase was extracted by CH_2Cl_2 (2 x 20 ml), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane 1:3) to yield the alcohol (0.121 g, 68%) as a colorless oil: IR ($CHCl_3$) 3467, 2962, 2931, 2873, 1716, 1612, 1514, 1462, 1248, 1179, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 6.98 (dd, J = 15.7, 7.6 Hz, 1H), 6.91-6.85 (m, 4H), 5.83 (d, J = 15.7 Hz, 1H), 5.48 (dd, J = 10.8, 9.6 Hz, 1H), 5.41-5.33 (m, 1H), 4.58 (d, J = 12.7 Hz, 1H), 4.46 (d, J = 11.9 Hz, 3H), 4.19 (q, J = 7.2 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.63-3.49 (m, 2H), 3.39-3.29 (m, 2H), 2.78 (dd, J = 15.7, 6.8 Hz, 1H), 2.61 (dd, J = 13.1, 6.6 Hz, 1H), 2.23-2.17 (m, 1H), 2.09-1.94 (m, 3H), 1.58-1.44 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 159.2, 151.1, 133.6, 131.1, 130.7, 129.5, 129.1, 128.7, 121.3, 114.0, 113.9, 113.8, 84.3, 81.6, 73.9, 71.6, 66.2, 60.4, 55.4, 39.7, 37.7, 34.8, 31.5, 23.8, 18.7, 15.1, 14.4, 11.5; LRMS (API-ES) 591.2 $(M+Na)^+$, 569.3 $(M+H)^+$, 551; $[\alpha]^{20}_D$ +37.2 (*c* 0.39, $CHCl_3$).

[00158] The same procedure for **45** was used with above alcohol (0.088 g, 0.16 mmol) to yield 64 mg (42% for 2 steps) of the **52** by flash column chromatography (EtOAc/hexane 1: 5): IR ($CHCl_3$) 2956, 2932, 2857, 1717, 1612, 1513, 1462, 1301, 1248, 1172, 1037, 835, 773cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.23 (m, 6H), 6.98 (dd, J = 15.9, 7.6 Hz, 1H),

6.89-6.85 (m, 6H), 6.40 (ddd, J = 16.8, 10.6, 10.5 Hz, 1H), 5.96 (apparent t, J = 10.9 Hz, 1H), 5.83 (d, J = 15.8 Hz, 1H), 5.47 (apparent q, J = 10.6 Hz, 1H), 5.36-5.24 (m, 4H), 5.15 (d, J = 16.8 Hz, 1H), 5.05 (d, J = 9.9 Hz, 1H), 4.58-4.32 (m, 6H), 4.20 (q, J = 7.1 Hz, 2H), 3.81 (s, 6H), 3.80 (s, 3H), 3.58-3.57 (m, 1H), 3.30-3.28 (m, 2H), 3.06-3.04 (m, 1H), 2.71-2.65 (m, 2H), 2.62-2.56 (m, 2H), 2.19-2.17 (m, 2H), 2.06-1.88 (m, 4H), 1.76-1.42 (m, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.07-0.97 (m, 12H), 0.92 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 159.2, 159.1, 151.2, 134.8, 133.8, 132.9, 132.5, 131.4, 130.7, 129.5, 129.2, 128.9, 128.6, 121.2, 117.3, 113.8, 113.7, 88.0, 81.6, 78.9, 74.9, 71.6, 70.9, 60.3, 55.4, 40.0, 39.7, 36.5, 35.5, 35.4, 31.6, 31.4, 26.3, 23.7, 20.8, 19.0, 18.8, 18.6, 17.2, 15.0, 14.4, 11.1, –3.2; LRMS (API-ES) 1034.2 $(M+K)^+$, 1017.6 $(M+Na)^+$, 995.7 $(M+H)^+$; $[\alpha]^{20}_D$ +40.7 (*c* 4.09, $CHCl_3$).

[00159] (*6R*,*7R*,*12S*,*13S*,*14S*,*19R*,*20R*,*21R*,*22S*)-21-(*tert*-Butyldimethylsilanyloxy)-7,13,19-tris-(4-methoxybenzyloxy)-6,12,14,20,22-pentamethylhexacosa-2,4,10,15,23,25-hexaenoic acid methyl ester (53). To the above ester **52** (64 mg. 64 μmol) in CH_2Cl_2 (2 ml) was added DIBAL-H (0.16 ml, 0.16 mmol, 1.0 M solution in hexane) at –78 °C dropwise and then warmed up to 0 °C and stirred for 1 h. The reaction mixture was quenched by EtOAc (2 ml) and sat'd sodium potassium tartrate solution (20 mL) followed by vigorously stirring for 4 h. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were washed with brine (10 mL). After drying over $MgSO_4$ and evaporation under vacuum, flash column chromatography (hexane/EtOAc 3:1) provided 47 mg of alcohol (77 %) as a colorless oil: IR ($CHCl_3$) 3429, 2956, 2857, 2360, 1613, 1513, 1463, 1248, 1037, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.37 (m, 6H), 7.03-6.98 (m, 6H), 6.53 (ddd, J = 16.8, 10.6, 10.5 Hz, 1H), 6.10 (apparent t, J = 11.0 Hz, 1H), 5.81-5.77 (m, 2H), 5.64 (d, J = 10.4 Hz, 1H), 5.57 (d, J = 10.9 Hz, 1H), 5.18 (d, J = 10.1 Hz, 1H), 4.72-4.45 (m, 6H), 4.21 (q, J = 3.2 Hz, 2H), 3.94 (s, 6H), 3.93 (s, 3H), 3.71 (dd, J = 5.6, 3.0 Hz, 1H), 3.41 (dd, J = 10.5, 5.2 Hz, 1H), 3.33 (dd, J = 11.1, 6.4 Hz, 1H), 3.19 (dd, J = 12.1, 5.9 Hz, 1H), 2.36-2.19 (m, 2H), 2.12-2.02 (m, 3H), 1.87-1.59 (m, 5H), 1.16-1.13 (m, 9H), 1.07-1.05 (m, 6H), 1.04 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 159.2, 159.1, 135.1, 134.8, 133.9, 132.7, 132.6, 131.5, 131.1, 129.7, 129.5, 129.3, 129.2, 128.8, 128.6,, 117.4, 114.1, 113.8, 88.1, 82.5, 79.0, 74.9, 71.5, 70.9, 65.2, 64.0, 55.4, 40.0, 39.4, 36.6, 35.6, 35.4, 31.4, 29.9, 26.4, 23.9, 23.7, 19.1, 18.8, 18.7, 17.3, 16.1, 11.1, –3.1, –3.2; LRMS (API-ES) 991.6 $(M+K)^+$, 975.6 $(M+Na)^+$; $[\alpha]^{20}_D$ +38.3 (*c* 1.05, $CHCl_3$).

[00160] The above alcohol (47 mg, 49 μmol) in CH_2Cl_2 (2 mL) was treated with Dess-Martin periodinane (31 mg, 73 μmol). After 2 h, the mixture was quenched with saturated $NaHCO_3$ (5 mL). The aqueous layer was extracted with ethyl ether (5 mL x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 3:1) to remove the residue from Dess-Martin reagent provided crude aldehyde as a colorless oil which was used for the next reaction without further purification. To a stirred solution of bis(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl) phosphate (0.013 ml, 59 μmol), 18-crown-6 (0.065 g, 0.25 mmol) in THF (1 ml) cooled to –78 °C was added dropwise potassium bis(trimethylsilyl)amide (0.12 ml, 59 μmol, 0.5M solution in toluene). Thereafter the above aldehyde in THF (1 ml) was added and the solution was stirred for 6 h at –78 °C. The reaction mixture was quenched by addition of a sat'd NH_4Cl solution (1 ml) and diluted with diethyl ether (10 ml). The layer was separated and organic phase was washed with brine (10 ml) and dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/Hexane 1:5), yielding 40 mg of (*E,Z*)-doubly unsaturated ester **53** (85% for 2 steps): IR ($CHCl_3$) 2956, 2856, 1717, 1612, 1513, 1462, 1301, 1248, 1173, 1037, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 15.4, 11.3 Hz, 1H), 7.43-7.37 (m, 6H), 7.03-6.98 (m, 6H), 6.68 (dd, *J* = 11.4, 11.3 Hz, 1H), 6.53 (ddd, *J* = 17.0, 10.7, 10.4 Hz, 1H), 6.19 (dd, *J* = 15.4, 7.6 Hz, 1H), 6.09 (apparent t, *J* = 11.2 Hz, 1H), 5.73 (d, *J* = 11.4 Hz, 1H), 5.64 (d, *J* = 10.3 Hz, 1H), 5.56 (d, *J* = 11.0 Hz, 1H), 5.45-5.41 (m, 3H), 5.28 (d, *J* = 15.3 Hz, 1H), 5.18 (d, *J* = 10.0 Hz, 1H), 4.71-4.45 (m, 6H), 3.94 (s, 6H), 3.93 (s, 3H), 3.87 (s, 3H), 3.70 (dd, *J* = 6.1, 3.2 Hz, 1H), 3.44-3.38 (m, 1H), 3.19 (dd, *J* = 6.9, 4.2 Hz, 1H), 2.85-2.77 (m, 3H), 2.34-2.31 (m, 2H), 2.08-2.04 (m, 3H), 1.84-1.55 (m, 5H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.14 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 8.2 Hz, 3H), 1.07-1.01 (m, 15H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.1, 158.9, 147.6, 145.6, 134.7, 133.7, 132.7, 132.4, 131.3, 130.9, 130.8, 129.5, 129.4, 129.0, 128.9, 128.4, 126.4, 117.2, 115.4, 113.7, 87.9, 82.1, 78.8, 74.7, 71.4, 70.8, 55.2, 53.4, 51.1, 40.0, 36.4, 35.4, 35.2, 31.4, 31.3, 29.7, 26.2, 23.7, 23.6, 18.9, 18.6, 18.5, 17.1, 15.4, 10.9, –3.3, –3.4; LRMS (API-ES) 1045.5 $(M+K)^+$, 1029.5 $(M+Na)^+$; $[\alpha]^{20}_D$ +35.3 (*c* 0.96, $CHCl_3$).

[00161] (7*R*,8*R*,13*S*,14*S*,15*S*,20*R*,21*R*,22*R*,23*S*)-8,14,20-Trihydroxy-7,13,15,21-tetramethyl-22-(1-methylpenta-2,4-dienyl)-oxacyclodocosa-3,5,11,16-tetraen-2-one (54). To a stirred solution of protected alcohol **53** (33 mg, 33 μmol) in THF (1 ml) at 0 °C was added 2 ml of 3 N HCl (prepared by adding 25 ml of conc. HCl to 75 ml MeOH). After 6 h,

the reaction mixture was diluted with EtOAc (5 ml) and H_2O (5 ml) and the organic phase was separated and aqueous phase was extracted with EtOAc (2 x 5 ml). The combined organic phase was washed with sat'd $NaHCO_3$ (10 ml), dried with $MgSO_4$, concentrated and the residue was purified by flash chromatography (EtOAc/Hexane 1:4) to yield 19 mg (21 μmol) of product (63%): IR ($CHCl_3$) 3491, 2958, 2869, 1716, 1612, 1513, 1456, 1248, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (dd, J = 15.3, 11.5 Hz, 1H), 7.29-7.22 (m, 6H), 6.92-6.84 (m, 6H), 6.61 (ddd, J = 17.7, 10.7, 10.4 Hz, 1H), 6.54 (dd, J = 11.5, 11.4 Hz, 1H), 6.10 (apparent t, J = 11.0 Hz, 1H), 6.06 (dd, J = 15.1, 7.7 Hz, 1H), 5.59 (d, J = 11.3 Hz, 1H), 5.49 (d, J = 10.4 Hz, 1H), 5.41 (d, J = 10.6 Hz, 1H), 5.37-5.30 (m, 3H), 5.21 (d, J = 17.0 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 4.58-4.34 (m, 6H), 3.81 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.47-3.44 (m, 2H), 3.31-3.25 (m 1H), 3.05 (dd, J = 7.3, 4.0 Hz, 1H), 2.80-2.69 (m, 2H), 2.66-2.61 (m, 1H), 2.20-2.15 (m, 2H), 2.05-1.91 (m, 3H), 1.85-1.76 (m, 1H), 1.72-1.61 (m, 2H), 1.57-1.47 (m, 2H), 1.09 (d, J = 6.8 Hz, 3H), 1.00 (apparent q, J = 7.1 Hz, 9H), 0.91 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 159.3, 159.1, 147.7, 145.7, 136.8, 134.1, 132.8, 132.5, 131.4, 132.8, 132.5, 131.4, 130.9, 130.4, 130.2, 129.6, 129.3, 128.3, 126.6, 118.0, 115.6, 114.0, 113.9, 88.1, 83.1, 82.2, 75.0, 71.5, 71.0, 55.4, 51.2, 40.1, 36.7, 36.3, 35.9, 35.4, 31.6, 30.6, 29.9, 23.9, 23.8, 19.0, 17.6, 15.6; LRMS (API-ES) 915.5 $(M+Na)^+$; $[\alpha]^{20}_D$ +41.1 (*c* 0.45, $CHCl_3$).

[00162] To the stirried solution of above ester (19 mg, 21 μmol) in EtOH (1 ml) was added 1N aqueous KOH solution (0.056 ml) and the mixture was refluxed gently until the ester disappeared (about 6 h) as determined by TLC. The ethanolic solution was concentrated and then diluted with EtOAc (2 ml). After the solution was acidified to pH3 with 1N HCl solution, organic phase was separated and aqueous phase was extracted with EtOAc (2 x 5 ml). The combined organic phase were dried with $MgSO_4$, concentrated and used as crude without further purification. The same procedure for **43** was used with above acid compound to yield 14 mg (79% for 2 steps) of the macrolactone product by flash column chromatography (EtOAc/hexane 1:3): IR ($CHCl_3$) 2961, 2869, 1708, 1612, 1513, 1462, 1248, 1174, 1076, 1036, 820, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.38 (m, 7H), 7.03-6.96 (m, 6H), 6.73-6.57 (m, 1H), 6.67 (apparent t, J = 11.2 Hz, 1H), 6.31 (dd, J = 15.8, 6.4 Hz, 1H), 6.12 (apparent t, J = 11.0 Hz, 1H), 5.69 (d, J = 11.1 Hz, 1H), 5.53-5.40 (m, 3H), 5.34-5.19 (m, 4H), 4.70-4.47 (m, 6H), 3.94 (s, 6H), 3.89 (s, 3H), 3.43-3.38 (m, 1H), 3.26-3.16 (m 2H), 3.08-3.03 (m, 1H), 2.87-2.86 (m, 1H), 2.78-2.73 (m, 2H), 2.22-2.19 (m, 2H), 2.07-2.05 (m, 3H), 1.93-1.55 (m, 5H), 1.23 (d, J = 6.9 Hz, 3H), 1.19 (d, J = 7.2 Hz, 9H), 1.07 (d, J =

6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 159.2, 158.9, 145.4, 143.6, 134.0, 133.0, 132.2, 131.4, 130.8, 130.7, 129.9, 129.53, 128.48, 129.43, 129.4, 129.3, 129.2, 129.0, 126.2, 117.7, 116.9, 113.8, 113.6, 88.0, 83.2, 75.2, 71.7, 71.2, 55.2, 39.4, 38.4, 37.0, 35.6, 34.3, 31.7, 25.4, 24.9, 19.7, 18.6, 17.2, 15.4, 10.0; LRMS (API-ES) 899.5 $(M+K)^+$, 883.5 $(M+Na)^+$; $[\alpha]^{20}_D$ +40.4 (*c* 0.47, $CHCl_3$).

[00163] The same procedure for **43** was used with above lactone (14 mg, 16 μmol) to yield 3.7 mg (46%) of the product **54** by flash column chromatography (EtOAc/hexane 1:2): IR ($CHCl_3$) 3411, 2964, 2926, 2872, 1692, 1637, 1435, 1182, 999, 962 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.27 (ddt, *J* = 15.7, 11.2, 1.2 Hz, 1H), 6.61 (ddt, *J* = 16.8, 1.1, 10.7 Hz, 1H), 6.53 (apparent t, *J* = 11.3 Hz, 1H), 6.02 (dd, *J* = 15.4, 6.7 Hz, 1H), 6.01 (apparent t, *J* = 11.0 Hz, 1H), 5.56 (d, *J* = 11.5 Hz, 1H), 5.43 (dd, *J* = 10.8, 9.1 Hz, 1H), 5.39-5.36 (m, 1H), 5.33 (apparent t, *J* = 10.6 Hz, 1H), 5.30-5.23 (m, 2H), 5.19 (dt, *J* = 16.8, 0.9 Hz, 1H), 5.10 (d, *J* = 10.1 Hz, 1H), 5.00 (dd, *J* = 7.8, 3.2 Hz, 1H), 3.67 (ddd, *J* = 11.7, 5.8, 4.6 Hz, 1H), 3.41 (ddd, *J* = 8.9, 6.0, 2.4 Hz, 1H), 3.31 (dd, *J* = 7.0, 5.0 Hz, 1H), 3.06-3.00 (m, 1H), 2.68-2.61 (m, 2H), 2.41 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.20-2.11 (m, 2H), 1.82 (dt, *J* = 7.2, 3.2 Hz, 1H), 1.77-1.71 (m, 2H), 1.41-1.35 (m, 2H), 1.32-1.25 (m, 2H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 145.8, 143.5, 133.8, 132.3, 132.1, 131.5, 130.0, 129.8, 129.7, 127.0, 117.9, 117.2, 79.3, 73.1, 72.7, 42.8, 40.4, 36.7, 35.0, 34.9, 34.6, 33.7, 24.7, 24.0, 18.7, 17.8, 17.3, 15.3, 9.9; HRMS (EI) calcd for $C_{31}H_{47}O_4$ 482.3396 $(M-OH)^+$, found 482.3416; $[\alpha]^{20}_D$ +19.2 (*c* 0.24, $CHCl_3$).

[00164] 4(*R*)-Benzyl-3-[4-(2,2-dimethyl-[1,3(*S*)]dioxolan-4-yl)-3(*S*)-hydroxy-2(*R*)-methyl-butyryl]-oxazolidin-2-one (56). Diisopropylethylamine (13 ml) was added to a solution of propionyloxazolidinone (13.1 g) in anhydrous CH_2Cl_2 (250 ml) at 0 °C, followed by dropwise addition of nBu_2BOTf (1.0M in CH_2Cl_2, 68 ml). The solution was stirred for 1 h at 0 °C. A solution of crude aldehyde from **55** (8.9 g) prepared before in anhydrous CH_2Cl_2 (10 ml) was added slowly at –78 °C. After addition, the reaction mixture was warmed to 0 °C and stirred for 1 h then quenched with pH7 phosphate buffer (20 mL). A solution of hydrogen peroxide (30%, 40 mL) in MeOH (80 mL) was added at 0 °C and the mixture was allowed to stir for 1 h. The reaction mixture was extracted with CH_2Cl_2 (50 mL x 2) and dried over $MgSO_4$ followed by flash chromatography (EtOAc/hexane 1:1) to yield 20.7 g of product (98%): IR ($CHCl_3$) 3434, 2956, 2929, 2858, 1724, 1472, 1463, 1257, 1097, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ7.33 m, 3H), 7.22 (m 2H), 4.72 (ddd, *J* = 10.5, 6.9, 3.2 Hz, 1H),

4.35 (m, 1H), 4.23 (m, 3H), 4.12 (dd, J = 8.5, 6.5 Hz, 1H), 3.82 (ddd, J = 10.2, 7.0, 3.2 Hz, 1H), 3.61 (t, J = 7.7 Hz, 1H), 3.25 (dd, J = 13.4, 3.3 Hz, 1H), 2.82 (dd, J = 13.4, 9.4 Hz, 1H), 1.80 (ddd, J = 14.2, 9.7, 4.6 Hz, 1H), 1.68 (ddd, J = 10.8, 7.8, 3.0 Hz, 1H), 1.43 (s, 3H), 1.38 (s, 3H), 1.30 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 152.9, 134.9, 129.3, 128.8, 127.3, 108.6, 73.4, 69.5, 68.5, 66.0, 54.9, 42.4, 37.5, 26.8, 25.6, 14.1, 10.8; $[\alpha]^{20}_D$ – 28.1 (*c* 4.1, $CHCl_3$).

[00165] 6-(2,2-Dimethyl-[1,3(*S*)]dioxolan-4-yl)-5(*S*)-hydroxy-4(*R*)-methyl-hex-2-enoic acid ethyl ester (57). To a solution of RED-Al (4.6 ml) in THF (100 ml) at –78 °C was added aldol product **56** (5.39 g) in THF (10 ml) slowly over 10 min. The evolution of gas could be seen as the solution was stirred for 10~15 min at –78 °C. The reaction was then warmed to –50 °C and stirred between –55 and –40 °C for 1 h. The reaction was quenched at –50 °C with 100 ml of EtOAc and 10 ml of MeOH and then poured into a mixture of sat'd Rochelle salt (30 ml) and Et_2O (60 ml) and stirred at –20 °C for 10 min. The aqueous layer froze as a gel. The ether layer was separated and the aqueous layer rinsed quickly with Et_2O (2 x 30 ml). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude aldehyde was taken immediately on to the Wittig reaction. To a 200 ml of dry THF was added 3.26 ml of triethylphosphonoacetate, followed by 1.86 g of potassium *tert*-butoxide. The mixture was stirred at room temperature for 10 min before cooling to –78 °C. The crude aldehyde was added in 20 ml of THF and stirred overnight while warming to room temperature. The mixture was poured into 30 ml of brine, extracted with Et_2O (3 x 40 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Flash silica gel chromatography (hexane/EtOAc 3:2) provided 2.02 g (52% for 2 steps) of pure product as an colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ6.88 (dd, J = 15.8, 8.0 Hz, 1H), 5.83 (d, J = 15.8 Hz, 1H), 4.28 (m, 1H), 4.14 (q, J = 7.1 Hz, 1H), 4.03 (dd, J = 8.1, 6.0 Hz, 1H), 3.76 (m, 1H), 3.53 (t, J = 8.0 Hz, 1H), 2.48 (brs, 1H), 2.41 (m, 1H), 1.72~1.56 (m, 2H), 1.37 (s, 3H), 1.31 (s, 3H),1.24 (t, J = 7.1 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 150.3, 121.6, 108.6, 73.5, 71.3, 69.3, 60.2, 42.8, 37.2, 25.8, 25.5, 14.5, 14.1.

[00166] 5(*S*),7(*S*),8-Tris-(*tert*-butyl-dimethyl-silanyloxy)-4(*R*)-methyl-oct-2-enoic acid ethyl ester (58). To a stirred solution of conjugated ester **57** (1.73 g) in MeOH (20 ml) was added Dowex HCR-W2 ion-exchange resin (2.0 g, activated by aqueous 1N HCl for 24 h then filtered, MeOH as eluent) and stirred for 24 h. The resin was filtered and filtrate was concentrated and dried for 2 h *in vacuo*. The triol was then used in next step without further purification. To a stirred solution of triol and 2,6-lutidine (3.3 mL, 28.6 mmol) in CH_2Cl_2 (30

mL) at 0 °C was added TBDMSOTf (5.1 mL, 22.2 mmol) and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched by the addition of water (25 mL). The reaction mixture was extracted by CH_2Cl_2 and dried over $MgSO_4$ followed by the evaporation of the solvent under reduced pressure. The residue was purified by short column chromatography (hexane/EtOAc 9:1) whereupon the **58** (2.96 g, 81% for 2 steps) was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.04 (dd, J = 15.9, 6.7 Hz, 1H), 5.75 (dd, J = 15.9, 1.5 Hz, 1H), 4.16 (dq, J = 1.3, 7.1 Hz, 2H), 3.84 (quint, J = 3.6 Hz, 1H), 3.71 (m, 1H), 3.49 (dd, J = 10.1, 5.4 Hz, 1H), 3.36 (dd, J = 10.1, 5.8 Hz, 1H), 2.48 (m, 1H), 1.59~1.40 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.85 (m, 27H), 0.056 (s, 3H), 0.049 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 151.7, 120.8, 72.8, 71.4, 68.0, 60.0, 42.2, 39.5, 25.9, 25.7, 18.3, 18.1, 14.2, 13.3, –3.0, –3.6, –4.2, –4.5, –5.4.

[00167] 5(*S*),7(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-8-hydroxy-4(*R*)-methyl-oct-2-enoic acid ethyl ester (59) To a solution of TBS ether **58** (7.4 g, 12.9 mmol) in THF (10 ml) was slowly added HF-pyridine in pyridine (40 ml, prepared by slow addition of 12 ml pyridine to 3 ml HF-pyridine complex followed by dilution with 25 ml THF). The mixture was stirred overnight at room temperature and quenched with sat'd $NaHCO_3$ (100 ml). The aqueous layer was separated and extracted with Et_2O (3 x 50 ml). The combined organic layers were washed with sat'd $CuSO_4$ (3 x 50 ml), dried over $MgSO_4$, and concentrated. Flash column chromatography (EtOAc/Hexane 1:4) afforded 3.86 g (65%) of the alcohol **59**: IR ($CHCl_3$) 3492, 2956, 2930, 2857, 1722, 1472, 1367, 1256, 1092, 1039, 836, 775 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.01 dd, J = 15.9, 6.7 Hz, 1H), 5.75 (dd, J = 15.9, 1.5 Hz, 1H), 4.15 (dq, J = 1.2, 7.2 Hz, 2H), 3.75 (m, 1H), 3.56 (m, 1H), 3.40 (m, 1H), 2.44 (m, 1H), 1.85 (t, J = 5.9 Hz, 1H), 1.61 (ddd, J = 11.5, 6.4, 5.0 Hz, 1H), 1.50 (ddd, J = 13.0, 7.2, 5.8 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.85 (s,, 9H), 0.60 (s, 6H), 0.34 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 151.1, 121.1, 72.8, 71.0, 66.9, 60.1, 41.8, 38.7, 25.8, 18.0, 14.2, 13.3, –4.2, –4.3.

[00168] 5(*S*),7(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4(*R*)-methyl-8-oxo-oct-2-enoic acid ethyl ester (60). The alcohol **59** (3.86 g, 8.34 mmol) in CH_2Cl_2 (20 mL) was treated with Dess-Martin periodinane (5.3 g, 12.5 mmol). After 1 h, the mixture was quenched with saturated $NaHCO_3$ (50 mL). The aqueous layer was extracted with ethyl ether (20 mL x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography (hexane/EtOAc 4:1) to remove

the residue from Dess-Martin reagent provided the aldehyde as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ9.53 (s, 1H), 7.02 dd, J = 15.9, 6.6 Hz, 1H), 5.77 (dd, J = 15.9, 1.4 Hz, 1H), 4.15 (dq, J = 1.0, 7.2 Hz, 2H), 4.07 (ddd, J = 6.4, 4.8, 1.4 Hz, 1H), 3.84 (ddd, J = 8.6, 6.8, 4.4 Hz, 1H), 2.52 (m, 1H), 1.66 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H).

[00169] 5(*S*),7(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-10(*S*)-[2-(4-methoxy-benzyl)-5(*S*)-methyl-[1,3(*R*)]dioxan-4-yl]-4(*R*)-methyl-undeca-2,8-dienoic acid ethyl ester (61). NaHMDS (1.0 M in THF, 12.3 mL, 12.3 mmol) was slowly added to a solution of the salt **21** (8.72 g, 13.7 mmol) in dry THF (13.7 mL) at 0 °C. The resulting red solution was stirred at room temperature for 20 min. The mixture was cooled to –78 °C and a solution of the aldehyde **60** (5.03 g, 10.9 mmol) in THF (2.0 mL) was added dropwise. The mixture was stirred for 20 min at –78 °C and then warmed to room temperature. After 4 h at room temperature, the mixture was quenched with saturated NH_4Cl (20 mL) and extracted with ethyl ether (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, evaporated and the residue was flash column chromatographed (hexane/EtOAc 9:1) to yield **61** (5.65 g, 75 %) as a colorless oil: IR ($CHCl_3$) 2957, 2929, 2856, 1720, 1650, 1617, 1518, 1463, 1370, 1250, 1158, 1073, 1032, 836, 774 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ7.34 m, 2H), 6.99 (dd, J = 15.8, 6.9 Hz, 1H), 6.82 (m, 2H), 5.72 (dd, J = 15.8, 1.5 Hz, 1H), 5.36 (s, 1H), 5.32 (dd, J = 11.1, 8.6 Hz, 1H), 5.18 (t, J = 10.8 Hz, 1H), 4.55 (ddd, J = 12.6, 8.6, 4.1 Hz, 1H), 4.12 (m, 2H), 3.99 (d, J = 7.2, 2.1 Hz, 1H), 3.91 (m, 1H), 3.77 (s, 3H), 3.52 (dd, J = 9.3, 2.1 Hz, 1H), 2.64 (m, 1H), 2.37 (m, 1H), 1.64 (m, 1H), 1.46 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 6H), 0.86 (s, 18H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 159.7, 151.9, 133.8, 132.7, 131.3, 120.8, 113.4, 101.7, 83.6, 73.8, 71.9, 66.4, 60.0, 55.1, 43.6, 42.9, 34.2, 29.8, 26.0, 25.9, 18.1, 15.6, 14.2, 13.5, 11.2, –3.0, –3.8, –4.1, –4.5; HRMS (ESI) calcd for $C_{36}H_{66}O_7Si_2K$ 729.3984 $(M+K)^+$, found 729.4013 ; $[\alpha]^{20}_D$ –8.7 (*c* 6.8, $CHCl_3$).

[00170] 5(*S*),7(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-10(*S*)-[2-(4-methoxy-benzyl)-5(*S*)-methyl-[1,3(*R*)]dioxan-4-yl]-4(*R*)-methyl-undeca-2,8-dien-1-ol (62). To the stirried solution of ester **61** (3.13 g, 4.53 μmol) in EtOH (20 ml), THF (2 ml) was added 1N aqueous KOH solution (45 ml) and the mixture was refluxed gently until the ester disappeared (about 6 h) as determined by TLC. The ethanolic solution was concentrated and then diluted with EtOAc (50 ml). After the solution was acidified to pH 3 with 1N HCl solution, organic phase was separated and aqueous phase was extracted with EtOAc (2 x 10

ml). The combined organic phase were dried with $MgSO_4$, concentrated and used as crude in next step without further purification. The carboxylic acid was treated with NEt_3 (1.5 ml) and ethyl chloroformate (0.67 ml) in dry THF (50 ml) at –10 °C. After 15 min, the mixture was warmed to 0 °C and a solution of $NaBH_4$ (1.2 g) in H_2O (10 ml) were added. After 4h, the reaction was quenched by addition of sat'd Rochelle salt solution and Et_2O. The layers were separated and the organic layer was washed with H_2O, sat'd $NaHCO_3$ solution and brine, dried with $MgSO_4$. Rotary evaporation and silica column chromatography (hexane/EtOAc 4:1) gave product **62** (1.79 g, 61 %) as a colorless oil: IR ($CHCl_3$) 3433, 2957, 2929, 2856, 1617, 1518, 1462, 1388, 1250, 1074, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 6.84 (m, 2H), 5.63 (dd, J = 15.7, 6.2 Hz, 1H), 5.48 (dt, J = 16.0, 5.6 Hz, 1H), 5.37 (t, J = 10.6 Hz, 1H), 4.59 (m, 1H), 3.99 (m, 2H), 3.93 (m, 1H), 3.87 (m, 2H), 3.77 (s, 3H), 3.49 (dd, J = 9.6, 2.0 Hz, 1H), 2.68 (m, 1H), 2.31 (m, 1H), 1.79 (brs, 1H), 1.64 (m, 1H), 1.44 (m, 2H), 1.15 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.88 (m, 21H), 0.09 (s, 3H), 0.06 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 134.4, 134.3, 132.4, 131.5, 129.1, 127.4, 113.4, 101.5, 83.5, 73.8, 72.8, 66.5, 63.7, 55.2, 42.2, 34.1, 29.8, 26.1, 25.9, 18.14, 18.10, 15.5, 15.2, 11.3, –2.9, –4.1, –4.2; HRMS (ESI) calcd for $C_{36}H_{64}O_6Si_2Na$ 671.4139 $(M+Na)^+$, found 671.4141; $[\alpha]^{20}_D$ –14.0 (*c* 1.5, $CHCl_3$).

[00171] 4-[4(*S*),6(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-1(*S*),7(*R*)-dimethyl-10-trityloxy-deca-2,8-dienyl]-2-(4-methoxy-benzyl)-5(*S*)-methyl-[1,3(*R*)]dioxane (63). To a solution of alcohol **62** (0.105 g) in pyridine (1.6 ml) was added trityl chloride (0.094 g) and DMAP (0.041 g). The mixture was then refluxed for 18 h, cooled to ambient temperature and added to a solution of sat'd $CuSO_4$ (20 ml). The mixture was extracted with Et_2O (2 x 20 ml), washed sat'd $CuSO_4$ (2 x 20 ml). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Flash column chromatography (EtOAc/hexane 1: 9) provided product **63** (0.142 g, 99%) as a pale yellow oil: IR ($CHCl_3$) 2956, 2926, 2855, 1616, 1517, 1462, 1378, 1249, 1073, 835, 773, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (m, 6H), 7.51 (m, 2H), 7.40 (m, 9H), 6.93 (m, 2H), 5.91 (dd, J = 15.7, 6.5 Hz, 1H), 5.66 (dt, J = 15.5, 5.2 Hz, 1H), 5.55 (m, 1H), 5.53 (s, 1H), 5.39 (t, J = 10.2 Hz, 1H), 4.78 (dt, J = 3.1, 8.9 Hz, 1H), 4.10 (m, 3H), 3.80 (s, 3H), 3.70 (m, 3H), 2.85 (m, 1H), 2.45 (m, 1H), 1.78 (m, 1H), 1.65 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H), 1.08 (m, 24H), 0.28 (s, 3H), 0.27 (s, 3H), 0.25 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 146.8, 144.3, 135.0, 134.1, 132.4, 131.3, 128.6, 127.8, 127.6, 127.3, 127.1, 126.7, 126.3, 113.3, 101.5, 86.6, 83.4, 73.8, 72.7, 66.6, 65.0, 55.0, 43.5,

42.8, 34.2, 29.9, 26.1, 25.9, 18.1, 15.7, 14.5, 11.3, –2.9, –3.8, –4.1, –4.3; HRMS (ESI) calcd for $C_{55}H_{78}O_6Si_2K$ 929.4969 $(M+K)^+$, found 929.5008; $[\alpha]^{20}_D$ –7.3 (*c* 1.1, $CHCl_3$).

[00172] 7(*S*),9(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-3-(4-methoxy-benzyloxy)-2(*S*)(*S*),10(*R*)-trimethyl-13-trityloxy-trideca-5,11-dien-1-ol (64). To the PMB acetal **63** (3.75 g. 4.21 μmol) in CH_2Cl_2 (20 ml) was added DIBAL-H (21 ml, 21 mmol, 1.0 M solution in hexane) at –78 °C dropwise and then warmed up to 0 °C and stirred for 1 h. The reaction mixture was quenched by EtOAc (10 ml) and sat'd sodium potassium tartrate solution (50 mL) followed by vigorously stirring for 4 h. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were washed with brine (30 mL). After drying over $MgSO_4$ and evaporation under vacuum, flash column chromatography (hexane/EtOAc 4:1) provided **64** (2.78 g, 74 %) as a colorless oil: IR ($CHCl_3$) 3434, 2956, 2928, 2856, 1612, 1514, 1471, 1249, 1073, 836, 774, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 6H), 7.29 (m, 11H), 6.84 (m, 2H), 5.84 (dd, *J* = 15.7, 6.2 Hz, 1H), 5.57 (dt, *J* = 15,7, 5.4 Hz, 1H), 5.44 (t, *J* = 8.7 Hz, 2H), 4.63 (m, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.46 (d, *J* = 10.9 Hz, 1H), 3.94 (m, 1H), 3.80 (s, 3H), 3.57 (d, *J* = 4.8 Hz, 2H), 3.48 (m, 1H), 3.31 (m, 2H), 2.80 (m, 1H), 2.42 (m, 1H), 1.84 (m, 2H), 1.55 (ddd, *J* = 14.2, 10.1, 1.9 Hz, 1H), 1.40 (ddd, *J* = 13.9, 8.6, 2.0 Hz, 1H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.97 (m, 12H), 0.93 (s, 9H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.16 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 144.3, 134.0, 133.7, 131.5, 130.9, 129.3, 128.6, 127.9, 127.7, 127.2,126.8, 126.5, 113.6, 86.7, 84.0, 73.9, 73.0, 66.2, 65.8, 65.1, 55.2, 42.3, 42.2, 38.0, 35.1, 26.0, 25.9, 18.5, 18.2, 18.1, 14.8, 12.0, –2.9, –4.0, –4.19, –4.23; HRMS (ESI) calcd for $C_{55}H_{80}O_6Si_2K$ 931.5125 $(M+K)^+$, found 931.5152; $[\alpha]^{20}_D$ –21.4 (*c* 0.52, $CHCl_3$).

[00173] 9(*S*),11(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5(*R*)-(4-methoxy-benzyloxy)-4(*S*),6(*S*),12(*R*)-trimethyl-15-trityloxy-pentadeca-2,7,13-trienoic acid ethyl ester (65). The alcohol **64** (2.01 g, 2.25 μmol) in CH_2Cl_2 (20 mL) was treated with Dess-Martin periodinane (1.43 g, 3.4 μmol). After 1 h, the mixture was quenched with saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with ethyl ether (25 mL x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 3:1) to remove the residue from Dess-Martin reagent provided crude aldehyde as a colorless oil which was used for the next reaction without further purification. To a stirred solution of triethyl phosphonoacetate (0.51 ml, 2.6 □mol) in THF (20 ml) cooled to –78 °C was added dropwise potassium *tert*-butoxide (0.29 g, 2.5 □mol) and stirred for 30 min. Thereafter the above aldehyde in THF (5

ml) was added and the solution was stirred for 1 h at –78 °C, then 2 h at 0 °C. The reaction mixture was quenched by addition of a sat'd NH_4Cl solution (5 ml) and diluted with diethyl ether (20 ml). The layer was separated and organic phase was washed with brine (20 ml) and dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/Hexane 1:9), yielding 2.01 g of unsaturated ester **65** (93 % for 2 steps): IR ($CHCl_3$) 2956, 2929, 2856, 1718, 1650, 1612, 1514, 1448, 1250, 1180, 1074, 836, 774, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 6H), 7.34 (m, 11H), 7.09 (dd, *J* = 15.8, 7.1 Hz, 1H), 6.89 (m, 2H), 5.89 (dd, *J* = 15.7, 5.8 Hz, 1H), 5.78 (d, *J* = 15.8 Hz, 1H), 5.66 (dt, *J* = 6.0, 15.7 Hz, 1H), 5.45 (m, 2H), 4.66 (m, 1H), 4.51 (m, 2H), 4.23 (m, 2H), 3.99 (m, 1H), 3.83 (s, 3H), 3.66 (d, *J* = 5.3 Hz, 2H), 3.29 (t, *J* = 4.7 Hz, 1H), 2.79 (m, 1H), 2.65 (m, 1H), 2.49 (m, 1H), 1.60 (m, 1H), 1.48 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.01 (s, 9H), 1.00 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 158.9, 152.2, 144.3, 134.3, 133.9, 131.0, 130.5, 129.3, 128.6, 127.6, 126.7, 126.4, 120.2, 113.5, 107.0, 86.6, 85.5, 73.4, 72.8, 66.3, 65.1, 59.9, 55.1, 42.2, 38.9, 35.2, 26.0, 25.9, 18.2, 18.1, 14.6, 14.2, 13.7, –3.0, –4.1, –4.2, –4.3; HRMS (ESI) calcd for $C_{59}H_{84}O_7Si_2K$ 999.5393 $(M+K)^+$, found 999.5387; $[\alpha]^{20}_D$ + 4.6 (*c* 3.1, $CHCl_3$).

[00174] 9(*S*),11(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5(*R*)-(4-methoxy-benzyloxy)-4(*S*),6(*S*),12(*R*)-trimethyl-15-trityloxy-pentadeca-7,13-dienoic acid ethyl ester (66). To a stirred solution of unsaturated ester **65** (2.02 g, 2.10 □mol) in MeOH (10 ml), THF (1 ml) at 0 °C was added 0.25 g of $NiCl_2 \cdot 6H_2O$ then portionwise $NaBH_4$ (0.16 g). After 1 h, the reaction mixture was evaporated and filtered with Celite using Et_2O as an eluent (5 ml). The organic phase was concentrated and the residue was purified by flash chromatography (EtOAc/Hexane 1:9) to yield 1.96 g (2.04 μmol) of product **66** (97 %) as a colorless oil: IR ($CHCl_3$) 2956, 2929, 2856, 1735, 1613, 1514, 1479, 1448, 1374, 1249, 1174, 1072, 836, 773, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (m, 6H), 7.33 (m, 11H), 6.84 (m, 2H), 5.81 (dd, *J* = 15.7, 6.1 Hz, 1H), 5.65 (m, 1H), 5.45 (m, 2H), 4.65 (m, 1H), 4.56 (d, *J* = 10.9 Hz, 1H), 4.45 (d, *J* = 10.9 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.96 (m, 1H), 3.80 (s, 3H), 3.62 (m, 2H), 3.14 (m, 1H), 2.79 (m, 1H), 2.43 (m, 1H), 2.23 (m, 1H), 1.72 (m, 2H), 1.54 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.97 (s, 18H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.17 (s, 3H), 0.154 (s, 3H), 0.151 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 158.8, 144.4, 134.6, 133.6, 132.1, 131.2, 129.1, 128.7, 127.7, 126.8, 126.4, 103.4, 86.6, 86.1, 73.8, 72.8, 66.5, 65.2, 60.0, 55.1, 42.8, 42.3, 35.4,

35.1, 32.3, 29.4, 26.0, 25.9, 18.4, 18.1, 14.6, 14.2, 13.9, –2.9, –4.0, –4.1; HRMS (ESI) calcd for $C_{59}H_{86}O_7Si_2K$ 1001.5549 $(M+K)^+$, found 1001.5586; $[\alpha]^{20}_D$ – 9.8 (*c* 0.95, $CHCl_3$).

[00175] 4(*R*)-Benzyl-3-[9(*S*),11(*S*)-bis-(*tert*-butyl-dimethyl-silanyloxy)-5(*R*)-(4-methoxy-benzyloxy)-4(*R*),6(*S*),12(*S*)-trimethyl-15-trityloxy-pentadeca-7,13-dienoyl]-oxazolidin-2-one (68). To the stirred solution of ester **66** (1.61 g, 1.67 □mol) in EtOH (20 ml), THF (2 ml) was added 1N aqueous KOH solution (17 ml) and the mixture was refluxed gently until the ester disappeared (about 6 h) as determined by TLC. The ethanolic solution was concentrated and then diluted with EtOAc (20 ml). After the solution was acidified to pH3 with 1N HCl solution, organic phase was separated and aqueous phase was extracted with EtOAc (2 x 10 ml). The combined organic phase were dried with $MgSO_4$, concentrated and used as crude without further purification. A solution of the above acid and Et_3N (0.47 ml) in dry THF (17 ml) was cooled to –78 °C, treated dropwise with pivaloyl chloride (0.25 ml), stirred in the cold for 1 h, and warmed to 0 °C prior to the addition of the (*S*)-oxazolidinone **4** (0.30 g) and LiCl (0.21 g). This reaction mixture was stirred overnight at room temperature and diluted with water (10 ml). The separated aqueous phase was extracted with ether (2 x 10 ml) and the combined organic phase were dried and evaporated and flash column chromatography (EtOAc/hexane 1:4) gave the product **68** (1.52 g, 83%) as a colorless oil: IR ($CHCl_3$) 2956, 2856, 1785, 1701, 1612, 1513, 1449, 1385, 1249, 1074, 910, 836, 774, 734, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 6H), 7.30 (m, 10H), 7.24 (m, 6H), 6.78 (m, 2H), 5.75 (dd, *J* = 15.7, 6.2 Hz, 1H), 5.54 (dt, *J* = 15.5, 5.5 Hz, 1H), 5.41 (m, 2H), 4.62 (m, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.42 (d, *J* = 11.1 Hz, 1H), 4.16 (m, 2H), 3.91 (m, 1H), 3.75 (s, 3H), 3.56 (m 2H), 3.30 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.15 (dd, *J* = 6.7, 2.2 Hz, 1H), 2.85 (m, 2H), 2.77 (m, 2H), 2.37 (m, 1H), 1.78 (m, 2H), 1.61 (m, 3H), 1.44 (m, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H), 0.92 (m, 21H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 158.7, 153.2, 144.3, 135.3, 134.7, 133.6, 132.5, 131.2, 129.3, 129.1, 128.8, 128.6, 127.6, 127.2, 126.7, 126.2, 113.4, 86.5, 85.8, 73.7, 72.7, 66.4, 65.9, 65.1, 55.0, 42.8, 42.4, 37.8, 35.5, 34.9, 33.5, 28.7, 26.0, 25.9, 18.2, 18.1, 14.5, 13.9, –2.9, –4.0, –4.2; HRMS (ESI) calcd for $C_{67}H_{91}NO_8Si_2K$ 1132.5920 $(M+K)^+$, found 1132.5874; $[\alpha]^{20}_D$ +14.8 (*c* 0.61, $CHCl_3$).

[00176] 4(*R*)-Benzyl-3-[9(*S*),11(*S*)-bis-(*tert*-butyl-dimethyl-silanyloxy)-5(*R*)-(4-methoxy-benzyloxy)-2(*S*),4(*S*),6(*S*),12(*R*)-tetramethyl-15-trityloxy-pentadeca-7,13-dienoyl]-oxazolidin-2-one (69). NaHMDS (1.0 M in THF, 1.68 ml) was added at –78 °C to a solution of **68** (1.67 g) in THF (4 ml). After 30 min, the reaction mixture was treated with

MeI (0.29 ml) at –78 °C, stirred for an additional 4 h, quenched with sat'd aqueous NH_4Cl, and extracted with ether (2 x 10 ml). The combined organic layers were dried ($MgSO_4$), concentrated and purified by flash column chromatography (EtOAc/hexane 1:9) to give product **69** (1.05 g, 62%) as a colorless oil: IR ($CHCl_3$) 2957, 2929, 2856, 1783, 1697, 1513, 1449, 1385, 1249, 1074, 836, 774, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (m, 6H), 7.29 (m, 16H), 6.80 (m, 2H), 5.79 (dd, *J* = 15.6, 6.2 Hz, 1H), 5.56 (dt, *J* = 15.6, 5.7 Hz, 1H), 5.42 (m, 2H), 4.62 (m, 2H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.1 Hz, 1H), 4.17 (m, 1H), 4.05 (m, 1H), 3.92 (m, 1H), 3.77 (s, 3H), 3.58 (d, *J* = 5.2 Hz, 1H), 3.27 (m, 1H), 3.08 (dd, *J* = 6.3, 2.5 Hz, 1H), 2.77 (m, 2H), 2.38 (m,1H), 1.76 (m, 1H), 1.64 (m, 2H), 1.46 (m, 4H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.93 (m, 21H), 0.14 (s, 3H), 0.11 (s, 6H), 0.10(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 158.7, 152.8, 144.4, 135.3, 134.9, 133.6, 132.3, 131.3, 129.4, 128.9, 128.8, 128.6, 127.6, 127.2, 126.7, 126.3, 113.5, 86.6, 86.5, 74.0, 72.8, 66.5, 65.8, 65.2, 43.0, 42.5, 37.8, 35.4, 35.3, 33.0, 26.3, 26.0, 25.9, 18.3, 18.1, 17.4, 14.5, 14.2, –2.9, –4.0, –4.1, –4.2; HRMS (ESI) calcd for $C_{68}H_{93}NO_8Si_2K$ 1146.6077 $(M+K)^+$, found 1146.6079; $[\alpha]^{20}_D$ +16.7° (*c* 1.1, $CHCl_3$).

[00177] 9(*S*),11(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-5(*R*)-(4-methoxy-benzyloxy)-2(*S*),4(*S*),6(*S*),12(*R*)-tetramethyl-15-trityloxy-pentadeca-7,13-dien-1-ol (70). To a stirred solution of **69** (0.41 g, 0.37 mmol) in THF (1.5 ml) at 0 °C was added MeOH (0.015 ml) and $LiBH_4$ (0.81 ml, 2.0 M soln in THF) dropwise. After stirring 2 h at 0 °C, saturated sodium potassium tartrate (10 ml) was added dropwise. The reaction mixture was warmed to room temperature and extracted with CH_2Cl_2 (10 ml x 2). The combined organic layer were washed with brine (10 ml) and dried over anhydrous $MgSO_4$, evaporated and the residue was chromatographed (hexane/EtOAc 4:1) to yield **70** (0.30 g, 87 %) as a colorless oil: IR ($CHCl_3$) 3400, 2956, 2928, 2856, 1613, 1514, 1449, 1377, 1249, 1074, 836, 774, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (m, 6H), 7.29 (m, 11H), 6.84 (m, 2H), 5.78 (dd, *J* = 15.7, 6.0 Hz, 1H), 5.58 (dt, *J* = 15.7, 5.2 Hz, 1H), 5.46 (m, 1H), 5.35 (m, 1H), 4.59 (t, *J* = 9.5, Hz, 1H), 4.48 (q, *J* = 10.9 Hz, 2H), 3.92 (m, 1H), 3.79 (s, 3H), 3.57 (d, *J* = 5.5 Hz, 2H), 3.25 (m 2H), 3.03 (t, *J* = 4.5 Hz, 1H), 2.75 (m 1H), 2.41 (m, 1H), 1.75 (m, 1H), 1.55 (m, 2H), 1.32 (m, 2H), 1.17 (m, 2H), 1.07 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.94 (s, 9H), 0.91 (m, 12H), 0.72 (d, *J* = 6.6 Hz, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 144.4, 134.4, 133.4, 131.5, 131.4, 129.1, 128.7, 127.7, 126.8, 126.5, 113.6, 87.6, 86.8, 74.1, 73.0, 68.9, 66.5, 65.4, 55.2, 42.7, 42.4, 37.1, 35.0, 33.1,

26.0, 25.9, 18.9, 18.1, 15.8, 14.9, 14.7, –2.8, –4.0, –4.06, –4.10; HRMS (ESI) calcd for $C_{58}H_{86}O_6Si_2K$ 973.6301 $(M+K)^+$, found 973.6264; $[\alpha]^{20}_D$ –31.7 (*c* 1.3, $CHCl_3$).

[00178] {3(*R*)-[2-(4-Methoxy-phenyl)-5(*S*)-methyl-[1(*S*),3]dioxan-4-yl]-2-oxo-butyl}-phosphonic acid dimethyl ester (71). *n*-Butyllithium (4.5 ml, 1.6 M solution in hexane) was added dropwise to a stirred solution of dimethyl methanephosphonate (0.77 ml) in THF (7 ml) at –78 °C. After 1 h, a solution of the known weinreb amide (Smith, A.B. et al. *J. Am. Chem. Soc.* **2000**, *122*, 8654-8664) (0.46 g) in THF (0.5 ml) was added. After 30 min, the reaction was then allowed to warm to 0 °C and quenched by pouring into brine (100 ml) and extracted with EtOAc (2 x 50 ml). The combined extracts were washed with brine (50 ml), dried over $MgSO_4$ and concentrated *in vacuo*. Flash silica gel column chromatography (EtOAc) gave the desired product **71** (0.47 g, 85%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 2H), 6.89 (m, 2H), 5.50 (s, 1H), 4.14 (dd, *J* = 11.3, 4.7, Hz, 1H), 4.06 (dd, *J* = 10.0, 2.7 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.74 (s, 3H), 3.59 (t, *J* = 11.1 Hz, 1H), 3.42 (d, *J* = 14.5 Hz, 1H), 3.34 (d, *J* = 14.5 Hz, 1H), 3.20 (d, *J* = 14.5 Hz, 1H), 3.13 (d, *J* = 14.5 Hz, 1H), 3.02 (dq, *J* = 2.8, 7.0 Hz, 1H), 2.06 (m, 1H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 159.5, 130.4, 126.9, 113.1, 100.5, 82.1, 72.4, 54.9, 52.6, 48.6, 39.3, 37.6, 30.6, 11.6, 8.7

[00179] 13(*S*),15(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2-[2-(4-methoxy-benzyl)-5(*S*)-methyl-[1,3(*S*)]dioxan-4-yl]-9(*R*)-(4-methoxy-benzyloxy)-6(*S*),8(*S*),10(*S*),16(*R*)-tetramethyl-19-trityloxy-nonadeca-4,11,17-trien-3-one (72). The alcohol **70** (0.30 g, 0.32 μmol) in CH_2Cl_2 (10 mL) was treated with Dess-Martin periodinane (0.20 g, 0.47 μmol). After 1 h, the mixture was quenched with saturated $NaHCO_3$ (10 mL). The aqueous layer was extracted with ethyl ether (10 mL x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 4:1) to remove the residue from Dess-Martin reagent provided crude aldehyde as a colorless oil which was used for the next reaction without further purification. A mixture of ketophosphonate **71** (0.14 g) and $Ba(OH)_2$ (0.043 g, activated by heating to 100 °C for 1~2 h before use) in THF (2 ml) was stirred at room temperature for 30 min. A solution of the above aldehyde in wet THF (2 ml + 2 x 1 ml washings, 40:1 THF/H_2O) was then added and stirred for overnight. The reaction mixture was diluted with Et_2O (10 ml) and washed with sat'd $NaHCO_3$ (10 ml) and brine (10 ml). The organic solution was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was chromatographed (hexane/EtOAc 4.5:1) to yield **72** (0.34 g, 90 %) as a colorless oil: IR

($CHCl_3$) 2957, 2929, 2855, 1615, 1515, 1461, 1249, 1076, 1036, 835, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 6H), 7.38 (m, 2H), 7.28 (m, 12H), 6.89 (m, 2H), 6.78 (m, 2H), 6.22 (d, J = 15.6 Hz, 1H), 5.74 (dd, J = 15.7, 6.2 Hz, 1H), 5.57 (m, 1H), 5.45 (s, 1H), 5.38 (m, 2H), 4.60 (m, 1H), 4.52 (d, J = 11.0 Hz, 1H), 4.33 (d, J = 11.0 Hz, 1H), 4.12 (dd, J = 11.2, 4.5 Hz, 1H), 3.90 (m, 2H), 3.81 (s, 3H), 3.76 (s, 3H), 3.55 (m, 3H), 3.04 (m, 1H), 2.92 (m, 1H), 2.75 (m, 1H), 2.36 (m, 1H), 2.25 (quint, J = 7.2 Hz, 1H), 2.02 (m, 1H), 1.71 (m, 1H), 1.56~1.33 (m, 4H), 1.25 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 7.8 Hz, 3H), 0.95 (d, J = 7.1 Hz, 3H), 0.92 (m, 21H), 0.85 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 159.7, 158.8, 153.1, 144.3, 134.6, 133.6, 132.4, 131.2, 131.0, 129.1, 128.6, 127.7, 127.2, 126.8, 126.3, 126.0, 113.5, 113.4, 100.7, 86.6, 85.7, 82.8, 73.8, 72.8, 66.4, 65.2, 55.2, 47.0, 42.8, 42.4, 40.4, 35.5, 34.2, 32.8, 32.2, 26.0, 25.9, 19.2, 18.4, 18.3, 18.1, 14.5, 14.4, 12.4, 10.7, –2.9, –4.0, –4.1; HRMS (ESI) calcd for $C_{74}H_{104}O_9Si_2K$ 1231.6856 $(M+K)^+$, found 1231.6850; $[\alpha]^{20}_D$ +22.8 (*c* 0.88, $CHCl_3$).

[00180] 13(*S*),15(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2-[2-(4-methoxy-benzyl)-5(*S*)-methyl-[1,3(*S*)]dioxan-4-yl]-9(*R*)-(4-methoxy-benzyloxy)-6(*S*),8(*S*),10(*S*),16(*R*)-tetramethyl-19-trityloxy-nonadeca-11,17-dien-3-one (73). To a stirred solution of unsaturated ketone **72** (0.34 g, 0.29 μmol) in MeOH (4 ml), THF (0.5 ml) at 0 °C was added 0.034 g of $NiCl_2 \cdot 6H_2O$ then portionwise $NaBH_4$ (0.022 g). After 1 h, the reaction mixture was evaporated and filtered with Celite using Et_2O as a eluent (5 ml). The organic phase was concentrated and the residue was purified by flash chromatography (EtOAc/Hexane 1:4) to yield 0.31 g of product **73** (89 %) as a colorless oil: IR ($CHCl_3$) 2956, 2929, 2855, 1713, 1614, 1515, 1461, 1249, 1075, 1036, 835, 774, 706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 6H), 7.29 (m, 13H), 6.87(m, 2H), 6.80 (m, 2H), 5.75 (dd, J = 15.7, 6.1 Hz, 1H), 5.55 (m, 1H), 5.45 (s, 1H), 5.38 (m, 2H), 4.60 (m, 1H), 4.48 (d, J = 10.9 Hz, 1H), 4.36 (d, J = 10.9 Hz, 1H), 4.13 (dd, J = 11.2, 4.4 Hz, 1H), 3.93 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.55 (m, 2H), 2.99 (m, 2H), 2.70 (m, 2H), 2.45 (t, J = 7.0 Hz, 1H), 2.36 (m, 1H), 2.02 (m, 1H), 1.75 (m, 1H), 1.63 (m, 1H), 1.49 (m, 2H), 1.37 (m, 3H), 1.23 (d, J = 7.1 Hz, 3H), 1.02 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.91 (m, 21H), 0.81 (d, J = 6.8 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H), 0.12 (s, 3H), 0.09 (s, 6H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 159.8, 158.8, 144.6, 144.4, 134.9, 133.4, 132.3, 131.8, 131.5, 131.0, 129.0, 128.9, 128.7, 127.7, 127.6, 127.2, 126.8, 126.7, 126.3, 113.5, 100.8, 87.4, 86.7, 83.1, 74.0, 72.9, 66.6, 65.2, 55.22, 55.18, 48.3, 43.1, 42.5, 41.6, 38.3, 35.5, 32.7, 31.5, 31.3, 29.6, 26.1, 26.0, 19.0, 18.5, 18.1,

14.5, 14.1, 12.1, 9.7, –2.9, –4.0, –4.1, –4.2; HRMS (ESI) calcd for $C_{74}H_{108}O_9Si_2K$ 1233.7013 $(M+K)^+$, found 1233.7036; $[\alpha]^{20}_D$ +3.0 (*c* 1.7, $CHCl_3$).

[00181] 13(*S*),15(*S*)-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2-[2-(4-methoxy-benzyl)-5(*S*)-methyl-[1,3(*S*)]dioxan-4-yl]-9(*R*)-(4-methoxy-benzyloxy)-6(*S*),8(*S*),10(*S*),16(*R*)-tetramethyl-19-trityloxy-nonadeca-11,17-dien-3-ol (74). To a solution of **73** (0.27 g) in MeOH (4 ml) was added $NaBH_4$ (0.013 g) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was evaporated and water (5 ml) was added. The reaction mixture was extracted with ether (2 x 20 ml) and washed with brine (10 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/Hexane 1:4.5) to yield 0.19 g of major product **74** (71 %) and 0.069 g (25 %) of minor product as a colorless oil: (major isomer) IR ($CHCl_3$) 3533, 2956, 2929, 2855, 1614, 1515, 1462, 1250, 1072, 1036, 835, 774, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (m, 6H), 7.43 (m, 2H), 7.30 (m, 11H), 6.92 (m, 2H), 6.84 (m, 2H), 5.78 (dd, *J* = 15.6, 6.1 Hz, 1H), 5.61 (m, 1H), 5.57 (s, 1H), 5.43 (m, 2H), 4.65 (m, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.18 (dd, *J* = 11.2, 4.5 Hz, 1H), 3.95 (m, 1H), 3.84 (s, 3H), 3.82 (m, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.59 (m, 2H), 3.06 (m, 2H), 2.78 (m, 1H), 2.41 (m, 1H), 2.19 (m, 1H), 1.81 (m, 2H), 1.56 (dd, *J* = 13.8, 8.1 Hz, 3H), 1.44 (m, 3H), 1.34 (m, 3H), 1.08 (d, *J* = 7.0 Hz, 6H), 0.99 (d, *J* = 7.2 Hz, 3H), 0.96 (m, 18H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 6H), 0.16 (s, 3H), 0.14 (s, 6H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 158.8, 144.6, 144.4, 134.9, 133.4, 132.3, 131.5, 130.7, 129.0, 128.9, 128.7, 127.7, 127.6, 127.2, 126.8, 126.7, 126.3, 113.7, 113.5, 89.0, 87.5, 86.7, 76.7, 74.0, 73.1, 72.8, 66.6, 65.2, 55.2, 55.1, 43.1, 42.5, 41.8, 37.4, 35.5, 34.4, 32.9, 32.4, 30.4, 30.1, 26.0, 25.9, 19.2, 18.5, 18.1, 14.5, 14.1, 11.9, 5.7, –2.9, –4.0, –4.1, –4.2; HRMS (ESI) calcd for $C_{74}H_{108}O_9Si_2K$ 1235.7169 $(M+K)^+$, found 1235.7149; $[\alpha]^{20}_D$ +3.5 (*c* 0.6, $CHCl_3$).

[00182] 5,15(*S*),17(*S*)-Tris-(*tert*-butyl-dimethyl-silanyloxy)-11(*R*)-(4-methoxy-benzyloxy)-3(*S*)-[2-(4-methoxy-phenyl)-ethoxy]-2(*S*),4(*R*),8(*S*),10(*S*),12(*S*),18(*R*)-hexamethyl-21-trityloxy-heneicosa-13,19-dien-1-ol (76). To a stirred solution of **74** (0.19 g, 0.16 mmol) and 2,6-lutidine (0.037 mL, 0.32 mmol) in CH_2Cl_2 (16 mL) at 0 °C was added TBDMSOTf (0.055 mL, 0.24 mmol) and the reaction mixture was stirred for 2 h at ambient temperature. The reaction mixture was quenched by the addition of water (5 mL). The reaction mixture was extracted by CH_2Cl_2 and dried over $MgSO_4$ followed by the evaporation of the solution under reduced pressure. The residue was purified by short column chromatography (hexane/EtOAc 9:1). To a stirred solution of TBS protected acetal (0.20 g,

0.15 mmol) in anhydrous CH_2Cl_2 (3 mL), under an atmosphere of N_2 at 0 °C was added diisobutylaluminum hydride (1.0 M in THF, 1.5 mL, 1.5 mmol) dropwise, and the reaction mixture was stirred for additional 1 h at 0 °C. The reaction mixture was quenched by the careful addition of aqueous sat'd potassium sodium tartrate solution (10 mL). The reaction mixture was stirred for 3 h at room temperature. The organic layer was separated, and the water layer was extracted by CH_2Cl_2 (20 mL). The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the organic solution under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane 1:4) whereupon the pure compound **76** (0.19 g, 91 % for 2 steps) was obtained: IR ($CHCl_3$) 3466, 2955, 2928, 2856, 1613, 1514, 1462, 1249, 1072, 1037, 835, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.52 (m, 6H), 7.30 (m, 13H), 6.94 (m, 2H), 6.85 (m, 2H), 5.79 (dd, *J* = 15.7, 6.3 Hz, 1H), 5.59 (dt, *J* = 15.7, 5.9 Hz, 1H), 5.44 (m, 2H), 4.67 (m, 1H), 4.60 (s, 2H), 4.57 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 10.9 Hz, 1H), 3.97 (m, 1H), 3.91 (m, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.68 (m, 2H), 3.60 (d, *J* = 5.6 Hz, 1H), 3.52 (dd, *J* = 6.6, 4.3 Hz, 1H), 3.07 (m, 2H), 2.97 (brs, 1H), 2.80 (dd, *J* = 14.5, 6.7 Hz, 1H), 2.40 (m, 1H), 2.02 (m, 1H), 1.95 (ddd, *J* = 9.6, 6.9, 4.0 Hz, 1H), 1.81 (m, 1H), 1.71 (m, 1H), 1.56 (m, 3H), 1.47 (m, 3H), 1.33 (m, 2H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 6H), 1.00 (s, 9H), 0.97 (m, 21H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.17 (s, 3H), 0.15 (s, 3H), 0.14 (s, 3H), 0.137 (s, 3H), 0.133 (s, 3H), 0.127 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 158.8, 144.6, 144.4, 135.0, 133.6, 132.5, 131.4, 130.6, 129.2, 129.0, 128.9, 128.7, 127.7, 127.6, 126.8, 126.7, 126.3, 113.9, 113.5, 87.4, 86.7, 85.9, 75.3, 74.0, 73.6, 72.8, 66.6, 65.2, 65.1, 55.2, 55.1, 43.2, 42.5, 42.0, 41.5, 37.0, 35.6, 33.4, 32.9, 31.9, 30.1, 26.08, 26.05, 25.98, 19.4, 18.4, 18.1, 15.8, 14.4, 13.9, 10.0, –2.9, –3.7, –3.9, –4.1, –4.2, –4.4; HRMS (ESI) calcd for $C_{80}H_{124}O_9Si_3K$ 1351.8190 $(M+K)^+$, found 1351.8134; $[\alpha]^{20}_D$ –6.1 (*c* 0.48, $CHCl_3$).

[00183] 7,17(*S*),19(*S*)-Tris-(*tert*-butyl-dimethyl-silanyloxy)-5(*S*),13(*R*)-bis-(4-methoxy-benzyloxy)-4(*S*),6(*S*),10(*R*),12(*S*),14(*S*),20(*S*)-hexamethyl-23-trityloxy-tetracosa-1,3,15,21-tetraen (77). The alcohol **76** (0.17 g, 0.13 μmol) in CH_2Cl_2 (5 ml) was treated with Dess-Martin periodinane (0.081 g, 0.2 μmol). After 1 h, the mixture was quenched with saturated $NaHCO_3$ (5 ml). The aqueous layer was extracted with ethyl ether (5 ml x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 4.5:1) to remove the residue from Dess-Martin reagent provided crude aldehyde as a colorless oil which was used for the next reaction without further purification. To a stirred solution of

the above crude aldehyde and 1-bromoallyl trimethylsilane (160 mg, 0.65 mmol) in anhydrous THF (3 ml) under an atmosphere of N_2 at room temperature was added $CrCl_2$ (0.13 g, 1.1 mmol) and the mixture was stirred for additional 14 h at ambient temperature. The reaction mixture was diluted with hexane followed by filtration through celite. After the evaporation of the solvent under reduced pressure, the residue was purified by short silica gel column chromatography using EtOAc/hexane (1:9). The foregoing product in THF (3 ml) was cooled to 0 °C and NaH (95 % w/w, 64 mg, 2.56 mmol) was added in one portion. The ice bath was removed after 15 min and the mixture was stirred for 2 h at ambient temperature. The reaction mixture was cooled to 0 °C, quenched with H_2O (5 ml), extracted with ethyl ether (5 ml x 2). The combined organic layer was washed with brine and dried over $MgSO_4$ followed by the evaporation of the organic solution under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc 9:1) whereupon the pure compound **77** (122 mg, 72% for 3 steps) was obtained: IR ($CHCl_3$) 2955, 2928, 2856, 1613, 1514, 1462, 1249, 1072, 1039, 835, 773, 705 cm^{-1} ;^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 6H), 7.28 (m, 13H), 6.89 (m, 2H), 6.79 (m, 2H), 6.61 (ddd, J = 16.8, 10.7, 10.6 Hz, 1H), 6.04 (t, J = 10.8 Hz, 1H), 5.73 (dd, J = 15.6, 6.3 Hz, 1H), 5.61 (t, J = 10.4 Hz, 1H), 5.58 (m, 1H), 5.37 (m, 2H), 5.20 (d, J = 16.8 Hz, 1H), 5.11 (d, J = 10.1 Hz, 1H), 4.54 (m, 3H), 4.50 (d, J = 11.0 Hz, 1H), 4.37 (d, J = 10.8 Hz, 1H), 3.90 (m, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.62 (m, 1H), 3.54 (d, J = 5.3 Hz, 1H), 3.35 (dd, J = 7.7, 3.1 Hz, 1H), 3.00 (m, 2H), 2.73 (m, 1H), 2.31 (m, 1H), 1.69 (m, 4H), 1.43 (m, 8H), 1.14 (d, J = 6.8 Hz, 3H), 1.00 (d, J = 7.1 Hz, 3H), 0.96 (s, 9H), 0.92 (s, 3H), 0.91 (s, 3H), 0.89 (m, 6H), 0.83 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.4 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 158.8, 144.6, 144.4, 135.0, 134.6, 133.7, 133.4, 132.6, 132.4, 131.5, 131.4, 129.1, 129.0, 128.98, 128.94, 128.7, 127.7, 126.8, 126.3, 117.2, 113.7, 113.5, 87.3, 86.7, 84.3, 75.0, 74.0, 72.9, 72.8, 66.6, 65.2, 55.2, 55.1, 43.2, 42.6, 42.0, 40.6, 35.7, 35.3, 33.2, 32.8, 32.3, 30.1, 26.1, 26.0, 19.4, 18.8, 18.3, 18.2, 18.1, 14.4, 14.0, 13.9, –2.9, –3.6, –3.9, –4.1, –4.2, –4.4; $[\alpha]^{20}_D$ +2.5 (*c* 1.2, $CHCl_3$).

[00184] 7(*S*),9(*S*),19-Tris-(*tert*-butyl-dimethyl-silanyloxy)-13(*R*),21(*S*)-bis-(4-methoxy-benzyloxy)-6(*R*),12(*S*),14(*S*),16(*S*),20(*R*),22(*S*)-hexamethyl-hexacosa-2,4,10,23,25-pentaenoic acid methyl ester (79). A solution of **77** (18.6 mg) in CH_2Cl_2 (0.2 ml) was cooled to –78 °C and B-chlorocatecholborane (0.25 M in CH_2Cl_2, 0.17 ml) was added. The solution was stirred at –78 °C for 1 h followed by treatment with sat'd aqueous $NaHCO_3$ (1 ml). The resulting reaction mixture was then diluted with CH_2Cl_2 (10 ml) and

H_2O (3 ml). The layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (2 x 5 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash chromatography (hexane/EtOAc 4;1) on silica gel to yield **78** (9.4 mg) as a colorless oil. The alcohol **78** (20 mg, 0.018 μmol) in CH_2Cl_2 (0.5 mL) was treated with Dess-Martin periodinane (12 mg, 0.028 μmol). After 1 h, the mixture was quenched with saturated $NaHCO_3$ (1 ml). The aqueous layer was extracted with ethyl ether (3 ml x 2) and the combined extracts were dried over anhydrous $MgSO_4$. Filtration and concentration followed by short flash column chromatography filtration (hexane/EtOAc 4.5:1) to remove the residue from Dess-Martin reagent provided crude aldehyde as a colorless oil which was used for the next reaction without further purification. To a stirred solution of bis(2,2,2-trifluoroethyl)-(methoxycarbonylmethyl) phosphate (0.005 ml, 0.024 □mol), 18-crown-6 (0.024 g, 0.09 mmol) in THF (0.5 ml) cooled to –78 °C was added dropwise potassium bis(trimethylsilyl)amide (0.044 ml, 0.022 □mol, 0.5M solution in toluene). Thereafter the above aldehyde in THF (0.5 ml) was added and the solution was stirred for 6 h at –78 °C. The reaction mixture was quenched by addition of a sat'd NH_4Cl solution (1 ml) and diluted with diethyl ether (5 ml). The layers were separated and organic phase was washed with brine (5 ml) and dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/Hexane 1:9) yielding 17 mg of (*E,Z*)-doubly unsaturated ester **79** (82 % for 2 steps): IR ($CHCl_3$) 2956, 2929, 2856, 1720, 1613, 1514, 1462, 1249, 1173, 1075, 836, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 5H), 6.82 (m, 4H), 6.55 (ddd, J = 16.8, 10.8, 10.8 Hz, 1H), 6.38 (t, J = 11.4 Hz, 1H), 6.05 (dd, J = 15.4, 6.2 Hz, 1H), 5.98 (t, J = 11.0 Hz, 1H), 5.55 (t, J = 10.5 Hz, 1H), 5.48 (d, J = 11.5 Hz, 1H), 5.31 (m, 2H), 5.14 (d, J = 16.8 Hz, 1H), 5.05 (d, J = 10.1 Hz, 1H), 4.54 (m, 1H), 4.49 (m, 3H), 4.31 (d, J = 10.9 Hz, 1H), 3.87 (m, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.68 (s, 3H), 3.57 (m, 1H), 3.29 (dd, J = 7.7, 3.1 Hz, 1H), 2.94 (m, 2H), 2.68 (m, 1H), 2.48 (m, 1H), 1.65 (m, 3H), 1.43~1.28 (m, 6H), 1.20 (m, 2H), 1.08 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.1 Hz, 3H), 0.90 (s, 9H), 0.86 (m, 21H), 0.81 (d, J = 6.7 Hz, 3H), 0.71 (d, J = 6.4 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.0, 158.8, 147.7, 146.9, 145.8, 134.6, 133.5, 132.7, 132.5, 131.6, 131.4, 129.1, 128.9, 128.8, 128.7, 128.4, 127.9, 127.7, 127.3, 126.4, 117.2, 114.9, 113.7, 113.6, 87.6, 84.3, 77.2, 74.9, 74.2, 72.9, 72.7, 66.4, 55.3, 55.2, 50.9, 43.1, 42.5, 42.1, 40.6, 35.8, 35.3, 33.6, 33.2, 32.9, 18.14, 18.11, 14.6, 13.9,

9.3, –2.9, –3.6, –3.9, –4.1, –4.4 ; HRMS (ESI) calcd for $C_{67}H_{114}O_9Si_3K$ 1185.7408 $(M+K)^+$, found 1185.7464; $[\alpha]^{20}_D$ –12.6 (*c* 0.75, $CHCl_3$).

[00185] 8(*S*),10(*S*),14(*R*),20-Tetrahydroxy-7(*S*),13(*S*),15(*S*),17(*R*),21(*S*)-pentamethyl-22(*S*)-(1(*S*)-methyl-penta-2,4-dienyl)-oxa-cyclodocosa-3,5,11-trien-2-one (83). The ester **79** (8.5 mg, 7.4 μmol) was dissolved in CH_2Cl_2 (1 ml) - H_2O (0.05 ml) and DDQ (5.0 mg, 22 μmol) was added at 0 °C. After 1 h of stirring at 0 °C, the reaction mixture was quenched by adding sat'd $NaHCO_3$ (5 ml). The organic phase was washed by sat'd $NaHCO_3$ solution (3 x 10 ml) and brine, dried over $MgSO_4$ and concentrated. Purification by flash column chromatography (EtOAc/hexane 1:4.5) furnished diol (6.4 mg, 95%) as a colorless oil. To the stirred solution of the above diol (6.4 mg, 7.06 μmol) in EtOH (0.7 ml) was added 1N aqueous KOH solution (0.07 ml) and the mixture was refluxed gently until the ester disappeared (about 7 h) as determined by TLC. The ethanolic solution was concentrated and then diluted with ether (4 ml). After the solution was acidified to pH3 with 1N HCl solution, organic phase was separated and aqueous phase was extracted with EtOAc (2 x 2 ml). The combined organic phase were dried with $MgSO_4$, concentrated and used as crude without further purification. A solution of above dihydroxy acid in THF (0.5 ml) was treated at 0 °C with Et_3N (0.006 ml, 43 μmol) and 2,4,6-trichlorobenzoyl chloride (0.0055 ml, 35 μmol). The reaction mixture was stirred at 0 °C for 30 min and then added to a 4-DMAP (3.5 ml, 0.02 M solution in toluene) at 25 °C and stirred for overnight. The reaction mixture was concentrated, EtOAc (5 mL) was added and the crude was washed with 1N HCl (2 x 5 ml), dried over $MgSO_4$. Purification by flash column chromatography (EtOAc/hexane 1:9) furnished macrolactone (3.0 mg, 49% for 2 steps) as a colorless oil. To a stirred solution of the above macrolactone (2.7 mg, 3.1 μmol) in MeOH (0.5 ml) at 0 °C was added 0.5 ml of 3 N HCl (prepared by adding 25 ml of conc. HCl to 75 ml MeOH). After 2 h at room temperature, the reaction mixture was diluted with EtOAc (2 ml) and H_2O (2 ml) and the organic phase was separated and aqueous phase was extracted with EtOAc (2 x 2 ml). The combined organic phase was washed with sat'd $NaHCO_3$ (5 ml), dried with $MgSO_4$, concentrated and the residue was purified by flash chromatography (EtOAc/Hexane 1:1) to yield **83** (1.2 mg, 73%): IR ($CHCl_3$) 3400, 2960, 2926, 2854, 1693, 1635, 1599, 1461, 1378, 1277, 1183, 1075, 964 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.34 (dd, *J* = 15.3, 11.3 Hz, 1H), 6.64 (ddd, *J* = 16.9, 10.5, 10.3 Hz, 1H), 6.57 (t, *J* = 11.4 Hz, 1H), 5.96 (t, *J* = 10.9 Hz, 1H), 5.95 (dd, *J* = 15.3, 8.3 Hz, 1H), 5.48 (t, *J* = 10.0 Hz, 1H), 5.47 (d, *J* = 11.6 Hz, 1H), 5.38 (dd, *J* = 11.1, 8.9 Hz, 1H), 5.27 (t, *J* = 10.5 Hz, 1H), 5.16 (d, *J* = 16.9 Hz, 1H), 5.08 (d, *J* = 10.2

Hz, 1H), 5.02 (dd, J = 8.0, 3.5 Hz, 1H), 4.65 (dt, J = 3.1, 8.4 Hz, 1H), 3.72 (ddd, J = 9.0, 6.3, 2.8 Hz, 1H), 3.25 (ddd, J = 10.2, 7.4, 2.8 Hz, 1H), 3.16 (dd, J = 5.4, 3.4 Hz, 1H), 3.06 (dd, J = 16.3, 8.3 Hz, 1H), 2.72 (ddd, J = 10.2, 6.7, 6.6 Hz, 1H), 2.36 (dd, J = 14.7, 7.2 Hz, 1H), 1.86 (dt, J = 6.6, 3.1 Hz, 1H), 1.81 (ddd, J = 10.5, 6.8, 3.7 Hz, 1H), 1.69 (m, 2H), 1.58 (m, 1H), 1.47 (ddd, J = 13.8, 9.5, 3.5 Hz, 1H), 1.37 (m, 1H), 1.25 (m, 1H), 1.17 (m, 1H), 1.13 (m, 1H), 1.09 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.9 Hz, 6H), 0.98 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 147.2, 145.3, 134.39, 134.37, 132.5, 132.3, 130.0, 127.6, 117.8, 116.5, 80.0, 75.4, 74.9, 72.0, 66.2, 43.2, 41.5, 40.7, 40.6, 35.6, 35.4, 35.0, 33.0, 31.2, 30.4, 20.4, 18.1, 17.3, 16.2, 12.4, 10.2 ; LRMS (ESI) calcd for $C_{32}H_{52}O_6$ 571.3 $(M+K)^+$, found 571.3; $[\alpha]^{20}_D$ +32.6 (*c* 0.10, MeOH).

[00186] ***(Z)*-(*4R,5S,6S,7S*)-*tert*-butyl-{6-(3, 4-dimethoxybenzyloxy)-4-[4-(4, 4, 5, 5, 6, 6, 7, 7, 8, 8, 9, 9, 10, 10, 11, 11, 11-heptadecafluoroundecyloxy)-benzyloxy]-5, 7-dimethylundec-8-enyloxy}dimethylsilane (85)**. A mixture solution of 84 (0.40 g, 0.39 mmol) in MeOH (8.0 ml) and CH_2Cl_2 (5.3 ml) was cooled to –78 °C and treated with a stream of ozone for 10 min. The reaction mixture was treated with dimethysulfide (2.0 ml) and pyridine (32 μl) and stirred for 3.0 h at ambient temperature. The reaction mixture was concentrated and diluted with Et_2O (80 ml). The organic layer was washed with saturated aqueous $CuSO_4$ (2X20 ml) and brine (20 ml), dried over $MgSO_4$, filtered and concentrated. At ambient temperature, a suspension of propyltriphenylphosphonium bromide (0.383 g 98 % purity, 0.97 mmol) in THF (15.0 ml) was added $NaN(TMS)_2$ (1.0 M solution in THF, 0.98 ml) at ambient temperature. After stirring 1 h, this solution was cooled to –78 °C. Then the crude residue in THF (2.0 ml) was introduced, and the resultant mixture was stirred for 3 h at –78 °C and was allowed to warm to ambient temperature for 12 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 ml) and extracted with Et_2O (2X40 ml). The combined extracts were washed with brine (20 ml), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10 % AcOEt/hexane) afforded **85** (0.08 g, 26 % yield): ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 6 H), 0.91 (s, 9 H), 0.93 (t, J = 7.6 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.06 (d, J = 6.8 Hz, 3 H), 1.47 (m, 2 H), 1.59 (m, 1 H), 1.66 (m, 1 H), 1.83 (m, 1 H), 1.94 (m, 2 H), 2.11 (m, 2 H), 2.33 (m, 2 H), 2.66 (m, 1 H), 3.35 (m, 1 H), 3.60 (t, J = 6.3 Hz, 2 H), 3.88 (s, 6 H), 4.04 (t, J = 5.8 Hz, 2 H), 4.38 (d, J = 11.3 Hz, 1 H), 4.48 (d, J = 10.9 Hz, 1 H), 4.53 (d, J = 10.9 Hz, 1 H), 4.59 (d, J = 11.3 Hz, 1 H), 5.35 (dt, J = 7.0, 10.3 Hz, 1 H), 5.42 (dd, J = 10.3, 10.1 Hz, 1 H), 6.82-7.02 (m, 4 H), 7.21-7.28 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.2, 10.3, 14.5, 18.4, 18.9, 20.6, 20.9, 25.9, 26.9, 28.0 (t, J = 22.5 Hz),

29.0, 34.9, 39.3, 55.8, 55.9, 63.2, 66.4, 70.8, 74.7, 79.4, 84.2, 110.5, 110.9, 114.3, 119.9, 106-122 (m), 129.6, 131.1, 131.3, 131.5, 131.6, 132.0, 148.4, 148.9, 158.2; IR (thin film/NaCl) cm^{-1} 2933, 2858, 1729, 1612, 1515, 1465, 1242, 1153, 1032, 834; MS (EI) *m/z* 1060 (M^+), 1035, 1003, 909, 567; $[\alpha]_D^{20}$ +2.37° (*c* 0.590, $CHCl_3$).

[00187] ***(4R,5S,6S,7S)*-*tert*-butyl-{6-(3, 4-dimethoxybenzyloxy)-4-[4-(4, 4, 5, 5, 6, 6, 7, 7, 8, 8, 9, 9, 10, 10, 11, 11, 12, 12, 13, 13, 13-heneicosafluorotridecyloxy)benzyloxy]-5, 7-dimethyl-non-8-enyloxy}dimethylsilane (84).** A solution of the alcohol (0.26 g, 0.57 mmol) and 1-bromomethyl-4-(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-heneicosafluorotridecyloxy)benzene (0.50 g, 0.66 mmol) in THF (6.0 ml) was cooled to –40 °C and ^{t}BuOK (1.0 M solution in THF, 0.70 ml) was added. The reaction mixture was stirred for 3.0 h. Then ^{t}BuOK (1.0 M solution in THF, 0.40 ml) was added again and the reaction solution was allowed to warm to ambient temperature for 9 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 ml) and extracted with Et_2O (2X40 ml). The combined extracts were washed with brine (20 ml), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10 % AcOEt/hexane) afforded **84** (0.326 g, 50 % yield): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.55 (s, 6 H), 0.91 (s, 9 H), 1.06 (apparent d, *J* = 6.8 Hz, 3 H), 1.49 (m, 2 H), 1.64 (m, 2 H), 1.93 (m, 1 H), 2.07 (m, 2 H), 2.21-2.48 (m, 3 H), 3.38 (m, 2 H), 3.61 (t, *J* = 6.1 Hz, 2 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.00 (t, *J* = 5.7 Hz, 2 H), 4.39 (d, *J* = 11.2 Hz, 1 H), 4.47 (d, *J* = 10.8 Hz, 1 H), 4.49 (d, *J* = 11.2 Hz, 1 H), 4.56 (d, *J* = 10.8 Hz, 1 H), 5.00 (m, 2 H), 5.92 (m, 1 H), 6.79-6.91 (m, 4 H), 7.27 (apparent d, *J* = 8.4 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 14.0, 17.3, 18.3, 20.6, 22.7, 25.9, 26.9, 28.0 (t, *J* = 22.2 Hz), 29.0, 38.5, 42.1, 55.7, 55.8, 63.1, 66.3, 70.9, 74.3, 79.9, 83.7, 110.9, 111.1, 114.3, 114.6, 119.9, 105-124 (m), 129.5, 131.6, 131.9, 141.2, 148.5, 148.9, 158.2; IR (thin film/NaCl) cm^{-1} 2928, 2858, 1611, 1515, 1242, 1154; MS (EI) *m/z* 1132 (M^+), 1075, 981, 817, 667, 465; $[\alpha]_D^{20}$ +3.15° (*c* 1.11, $CHCl_3$).

[00188] ***(Z)*-(*4R,5S,6S,7S*)-*tert*-Butyl-{6-(3, 4-dimethoxy-benzyloxy)-4-[4-(4, 4, 5, 5, 6, 6, 7, 7, 8, 8, 9, 9, 10, 10, 11, 11, 12, 12, 13, 13, 13-heneicosafluorotridecyloxy)benzyloxy]-9-iodo-5, 7-dimethylnon-8-enyloxy}dimethylsilane (86).** A mixture of **84** (0.326 g, 0.28 mmol) in MeOH (8.0 ml) and CH_2Cl_2 (6.0 ml) was cooled to –78 °C and treated with a stream of ozone for 5 min. The reaction mixture was treated with dimethylsulfide (1.5 ml) and pyridine (23 μl) and stirred for 3.0 h at ambient temperature. The reaction mixture was concentrated and diluted with Et_2O (80 ml). The organic layer was washed with saturated aqueous $CuSO_4$ (2X20 ml) and brine

(20 ml), dried over $MgSO_4$, filtered and concentrated. At ambient temperature, a suspension of (iodomethyl)triphenylphosphonium iodide (0.213 g, 0.40 mmol) in THF (3.0 ml) was added $NaN(TMS)_2$ (1.0 M solution in THF, 0.40 ml). After stirring 0.5 h, this solution was cooled to –78 °C. Then HMPA (0.13 ml) and the crude residue in THF (2.0 ml) were introduced, and the resultant mixture was stirred for 20 min at –78 °C and stirred at ambient temperature for 0.5 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 ml) and extracted with Et_2O (2X40 ml). The combined extracts were washed with brine (20 ml), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10 % AcOEt/hexane) afforded (*Z*)-(*4R,5S,6S, 7S*)-*tert*-butyl-{6-(3, 4-dimethoxy-benzyloxy)-4-[4-(4, 4, 5, 5, 6, 6, 7, 7, 8, 8, 9, 9, 10, 10, 11, 11, 12, 12, 13, 13, 13-heneicosafluorotridecyloxy)benzyloxy]-9-iodo-5, 7-dimethylnon-8-enyloxy}dimethylsilane (0.119 g, 33 % yield): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 1.23-1.77 (m, 5 H), 2.04 (m, 2 H), 2.23 (m, 2 H), 2.70 (m, 1 H), 3.44 (m, 2 H), 3.59 (t, *J* = 6.3 Hz, 2 H), 3.86 (s, 3 H), 3.87 (s, 3 H), 4.03 (t, *J* = 5.8 Hz, 2 H), 4.40 (d, *J* = 11.3 Hz, 1 H), 4.53 (s, 2 H), 4.57 (d, *J* = 11.3 Hz, 1 H), 6.15 (d, *J* = 7.3 Hz, 1 H), 6.28 (dd, *J* = 7.3, 9.0 Hz, 1 H), 6.80-6.89 (m, 4 H), 7.22-7.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2, 10.2, 14.2, 17.2, 18.4, 20.7, 22.8, 26.0, 27.3, 28.0 (t, *J* = 22.1 Hz), 29.8, 31.7, 40.2, 42.9, 51.4, 55.9, 56.0, 63.3, 66.4, 71.1, 75.4, 78.9, 82.2, 84.1, 107-122 (m), 110.9, 111.2, 114.4, 120.1, 129.5, 131.6, 131.8, 143.2, 148.6, 148.9, 158.2; IR (thin film/NaCl) cm^{-1} 2956, 2859, 1727, 1611, 1514, 1467, 1243, 1154, 856; MS (EI) *m/z* 1201(M^+-C_4H_9), 1107, 667; $[\alpha]_D^{20}$ +4.04° (*c* 1.01, $CHCl_3$).

[00189] (*Z*)-(*4R,5S,6S,7S*)-*tert*-butyl-{6-(3, 4-dimethoxybenzyloxy)-4-[4-(4, 4, 5, 5, 6, 6, 7, 7, 8, 8, 9, 9, 10, 10, 11, 11, 12, 12, 13, 13, 13-heneicosafluorotridecyloxy)benzyloxy]-5, 7-dimethyl-9-phenyl-non-8-enyloxy}dimethylsilane (87). To a solution of (*Z*)-(*4R,5S,6S,7S*)-*tert*-butyl-{6-(3,4-dimethoxy-benzyloxy)-4-[4-(4, 4, 5, 5, 6, 6, 7, 7, 8, 8, 9, 9, 10, 10, 11, 11, 12, 12, 13, 13, 13-heneicosafluorotridecyloxy)benzyloxy]-9-iodo-5, 7-dimethylnon-8-enyloxy}dimethylsilane (0.120 g, 0.09 mmol) and $Pd(PPh_3)_4$ (0.011 g, 0.01 mmol) in THF (1.0 ml) was added PhZnI (0.5 M solution in THF, 0.97 ml) at ambient temperature. After stirring for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 ml) and extracted with Et_2O (2X40 ml). The combined extracts were washed with brine (20 ml), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10 % AcOEt/hexane) afforded **87** (0.0726 g, 63 % yield): ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6 H), 0.95 (s, 9 H), 1.07 (d, *J* = 6.8

Hz, 3 H), 1.19 (d, J = 6.7 Hz, 3 H), 1.27-1.59 (m, 4 H), 1.85 (m, 1H), 2.13 (m, 2 H), 2.35 (m, 2 H), 3.11 (m, 2 H), 3.39 (brt, J = 5.2 Hz, 1 H), 3.57 (t, J = 6.2 Hz, 2H), 3.84 (s, 3 H), 3.91 (s, 3 H), 4.02 (d, J = 11.3 Hz, 1 H), 4.08 (t, J = 5.8Hz, 2 H), 4.32 (d, J = 11.3 Hz, 1 H), 4.52 (d, J = 10.6 Hz, 1 H), 4.67 (d, J = 10.6 Hz, 1 H), 5.83, (dd, J = 11.5, 11.5 Hz, 1 H), 6.53 (d, J = 11.5 Hz, 1 H), 6.86-7.37 (m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –5.2, 10.2, 14.2, 18.4, 18.9, 20.7, 22.8, 26.1, 27.3, 27.8 (t, J = 21.7Hz), 28.9, 31.7, 35.6, 39.7, 55.8, 56.0, 63.3, 66.4, 71.2, 75.2, 79.9, 84.6, 107-122 (m), 110.9, 111.2, 114.3, 120.0, 126.7, 128.3, 128.7, 128.9, 129.3, 131.9, 135.3, 137.8, 148.5, 148.9, 158.1; IR (thin film/NaCl) cm^{-1} 2926, 2857, 1727, 1515, 1464, 1242, 1154, 1031; MS (EI) *m/z* 1208 (M^+), 1151, 1066, 667; $[\alpha]_D^{20}$ +3.73° (*c* 0.805, $CHCl_3$).

[00190] [2*R*]-Butane-1,2,4-triol. To a dry 1L two-necked flask equipped with a pressure-equalizing addition funnel, a magnetic stirring bar and a reflux condenser was added THF (200 mL), $B(OMe)_3$ (100 mL), and (R)-(+)-malic acid (40.0 g, 0.30 mol). To this solution was added dropwise BH_3-SMe_2 (100 mL, 1.0 mol) over 2 h in a water bath as instantaneous H_2 evolution occurred throughout the addition. After stirring for 20 h at rt, MeOH (200 mL) was added dropwise, and the resulting solution was filtered through a glass frit funnel charged with Celite to remove any solids. The clear, yellow filtrate was concentrated *in vacuo* to give a yellow oil. The residue was dissolved in MeOH (100 mL) and concentrated *in vacuo*. This was repeated 5 times giving 26.9 g of the triol (85%). The spectral data matched that of the known compound.

[00191] [2*R*]-2-(4-Methoxyphenyl)-[1,3]dioxan-4-yl]methanol (88). A solution of the triol (5.0 g, 47.1 mmol), *p*-anisaldehyde (9.62 g, 70.7 mmol), PPTS (0.12 g, 0.047 mmol) in benzene (100 mL) was refluxed for 10 h with the azeotropic removal of H_2O. $NaHCO_3$ (0.20 g, 2.4 mmol) was added to the solution and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (20% to 50% EtOAc in hexanes) to give **88** (65%). ^{1}H NMR (300 MHz, $CDCl_3$) –7.41 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.49 (s, 1H), 4.28 (ddd, J = 11.1, 5.1, 1.3 Hz, 1H), 4.00-3.95 (m, 2H), 3.79 (s, 3H), 3.67-3.64 (m, 2H), 2.04 (br s, 1H), 1.91 (dq, J = 12.4, 5.1 Hz, 1H), 1.46-1.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) – 160.1, 132.0, 127.4, 113.6, 101.2, 76.6, 66.5, 65.6, 55.3, 26.9.

[00192] [2*R*]-*tert*-Butyl-[2-(4-methoxyphenyl)-[1,3]dioxan-4-ylmethoxy]diphenylsilane. A solution of alcohol **88** (8.13 g, 36.2 mmol), imidazole (3.9 g, 57.3 mmol), and TBDPSCl (10.2 mL, 39.7 mmol) in DMF (75 mL) was stirred overnight at room temperature under argon. A mixture of H_2O (250 mL) and EtOAc (150 mL) was added

and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined and washed with H_2O (2 x 100 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (20% EtOAc in hexanes) to yield 15.9 g (95%) of the silyl ether as a clear yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.41-7.34 (m, 8H), 6.86 (d, J = 8.8 Hz, 2H), 5.46 (s, 1H), 4.28 (dd, J = 11.0, 4.2 Hz, 1H), 4.02-3.96 (m, 2H), 3.86-3.83 (m, 1H), 3.79 (s, 3H), 3.67 (dd, J = 10.2, 5.6 Hz, 1H), 1.84 (dq, J = 12.2, 4.9 Hz, 1H), 1.65-1.61 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 135.7, 133.4, 130.0, 129.6, 128.2, 128.0, 113.4, 101.0, 77.5, 66.9, 66.0, 55.3, 28.1, 26.8, 19.3.

[00193] 4-(*tert*-Butyldiphenylsilanyloxy)-3-(4-methoxybenzyloxy)-butan-1-ol. To a stirred solution of the acetal (5.0 g, 10.8 mmol) in toluene (20 mL) at –78 °C was added slowly via cannula DibalH in toluene (33.0 mL, 1M). The reaction mixture was maintained at –78 °C for 12 h and quenched by slow addition to a vigorously stirred saturated solution of Rochelle salt in H_2O (70 mL). The emulsion was stirred until two layers formed (1 h). The aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL) and the organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash chromotaography (20% to 50% EtOAc in hexanes) providing 4.01 g (80%) of the corresponding alcohol as a clear, yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.69-7.66 (m, 4H), 7.43-7.38 (m, 6H), 7.20 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.60 (d, J = 11.2 Hz, 1H), 4.41 (d, J = 11.2 Hz, 1H), 3.79 (s, 3H), 3.77-3.66 (m, 5H), 1.82-1.79 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 135.5, 133.2, 129.4, 129.0, 128.0, 127.6, 113.8, 78.3, 72.1, 66.4, 60.2, 55.2, 34.2, 26.8, 19.1.

[00194] 4-(*tert*-Butyldiphenylsilanyloxy)-3-(4-methoxybenzyloxy)-butyraldehyde (89). DMSO (0.9 mL, 12.8 mmol) was added, dropwise, to a stirred solution of oxalyl chloride (0.5 mL, 6.0 mmol) in CH_2Cl_2 (8.0 mL) at –78 °C under argon. The reaction mixture was stirred for 5 min then a solution of the alcohol (2.04 g, 4.41 mmol) in CH_2Cl_2 (27.0 mL) was added dropwise. After 1h at –78 °C, Et_3N (3.15 mL, 22.4 mmol) was added slowly via syringe, the mixture was stirred for 5 min then warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with ice cold 0.5 M HCl (50 mL) then H_2O (40 mL) and the layers were separated. The aqueous layers were combined and extracted with CH_2Cl_2 (2 x 40 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The intermediate aldehyde **89** was used in the following reaction without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 7.67-7.63 (m, 4H),

7.44-7.34 (m, 6H), 7.16 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.52 (d, J = 11.1 Hz, 1H), 4.41 (d, J = 11.1 Hz, 1H), 4.03-3.99 (m, 1H), 3.81 (s, 3H), 3.79-3.74 (m, 2H), 3.68-3.63 (m, 1H), 2.67 (dd, J = 6.1, 1.9 Hz, 1H), 1.04 (s, 9H).

[00195] [3*R*,4*R*,6*R*]-7-(*tert*-Butyldiphenylsilanyloxy)-6-(4-methoxybenzyloxy)-3-methylhept-1-en-4-ol (90). A solution of (*R*,*R*)-diisopropyl tartrate (Z)-crotylboronate (15.0 mmol) was added to 4 Å powdered molecular sieves (0.170 g) in toluene(8.4 mL) under argon and the mixture was stirred for 20 min at room temperature. The mixture was cooled to –78 °C and a solution of the aldehyde **89** (2.0 g, 4.4 mmol) in toluene (5.0 mL) was added dropwise via cannula. The resulting mixture was maintained at –78 °C for 3 h and then treated with $NaBH_4$ (0.072 g, 1.75 mmol) in EtOH (2.0 mL) and warmed to 0 °C. The reaction mixture was treated with 1N NaOH (30 mL) and stirred vigorously for 30 min, followed by separation of the organic layer. The aqueous layer was extracted with CH_2Cl_2 (5 x 55 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (5% to 20% Et_2O in hexanes) providing 1.43 g (63% 2 seps) of alcohol, a clear oil: $[\alpha]^{20}{}_D$ = +0.32 (*c* 1.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 7.0 Hz, 2H), 7.45-7.35 (m, 6H), 7.20 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.73 (ddd, J = 18.2, 11.0, 7.4 Hz, 1H0, 5.03 (dd, J = 11.0, 1.7 Hz, 1H), 5.02 (dd, J = 18.2, 1.7 Hz, 1H), 4.59 (d, J = 11.3 Hz, 1H), 4.40 (d, J = 11.3 Hz, 1H), 3.79 (s, 3H), 3.89-3.75 (m, 2H), 3.68-3.65 (m, 2H), 2.18 (sext, J = 6.8 Hz, 1H), 1.84-1.55 (m, 2H), 1.05 (s, 9H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ159.0, 140.6, 135.6, 133.5 (2C), 130.3, 131.0, 127.6, 129.6, 114.4, 113.6, 72.2, 83.1, 64.1, 71.3, 55.2, 40.8, 37.2, 26.8, 19.2, 14.4; IR (thin film) 3056, 2989, 2859, 1513, 1426, 1248, 1112, 1077 cm^{-1}; LRMS (EI) 517 (M–H), 435, 333, 303, 255, 241, 223, 199, 135, 121 *m/z*.

[00196] [2R,4*R*,5*R*]-[2,4-bis-(4-Methoxybenzyloxy)-5-methylhept-6-enyloxy] *tert*-butyldiphenyl silane. A mixture of NaH (1.8 g, 7.23 mmol) in THF (5 mL) was cooled to 0°C then DMF (5 mL), the alcohol (1.25 g, 2.41 mmol) in THF (5 mL), and PMBBr (1.14 g, 6.03 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 48 h. The resulting mixture was poured into a pH 7 phosphate buffer and diluted with ether (85 mL). The organic layer was separated and washed with pH 7 buffer (3 x 55 mL), dried over K_2CO_3, filtered and concentrated *in vacuo*. The resulting crude yellow oil was purified by flash chromatography (5% to 10% EtOAc in hexanes) providing 0.985 g (64%) of the PMB ether a clear, yellow tinted oil: $[\alpha]^{20}{}_D$ = +0.31 (*c* 1.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H), 7.39-7.37 (m, 6H), 7.22-7.19 (m, 4H), 6.86-6.84 (m, 4H), 5.73

(ddd, J = 17.8, 9.8, 7.0 Hz, 1H), 5.04-4.99 (m, 2H), 4.64 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.1 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.18 (d, J = 11.1 Hz, 1H), 3.78 (s, 6H), 3.81-3.52 (m, 4H), 2.60-2.56 (m, 1H), 1.57-1.51 (m, 2H), 1.05 (s, 9H), 1.0 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 140.6, 135.6, 133.5 (2C), 130.3, 131.0, 127.6, 129.6, 114.4, 113.6, 72.2, 83.1, 64.1, 75.4, 55.2, 40.8, 37.2, 26.8, 19.2, 14.4, –5.3; IR (thin film) 3055, 2985, 1422, 1280, 247 cm^{-1}; LRMS (EI) 581.34 (M–C_4H_7), 579.34, 522.34, 444, 326, 383, 323, 339, 301, 255, 137, 122 *m/z*.

[00197] [2*R*,3*R*,5*R*]-6-(*tert*-Butyldiphenylsilanyloxy)-3,5-bis-(4-methoxybenzyloxy)-2-methylhexanal. To a solution of MeOH (30 mL), CH_2Cl_2 (10 mL) and a few drops of pyridine was added the PMB ether (800 mg, 1.25 mmol) and the mixture was cooled to –78°C. Ozone was bubbled through the reaction mixture until a slight purple color was seen. Excess DMS (6.0 mL) was added to the solution and allowed to warm to RT. After 3 h, the mixture was concentrated in vacuo. The yellow residue was dissolved in hexanes (60 mL) and washed with H_2O (2 x 40 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the intermediate aldehyde (800 mg, 1.25 mmol) that was used in the following step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, J = 2.0, 1H), 7.69-7.65 (m, 4H), 7.39-7.37 (m, 6H), 7.22-7.19 (m, 4H), 6.86-6.84 (m, 4H), 4.64 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.1 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.18 (d, J = 11.1 Hz, 1H), 3.78 (s, 6H), 3.81-3.52 (m, 4H), 2.60-2.56 (m, 1H), 1.57-1.51 (m, 2H), 1.05 (s, 9H), 1.0 (d, J = 6.9 Hz, 3H).

[00198] [4*R*,5*R*,7*R*]-8-(*tert*-Butyldiphenylsilanyloxy)-5,7-bis-(4-methoxybenzyloxy)-4-methyloct-2-enoic acid ethyl ester (91). To a stirred suspension of NaH (36 g, 1.56 mmol) in toluene (10 mL) at 0° C and under argon was added a solution of 2-(diethoxyphosphoryl)propionic acid ethyl ester (0.47 mL, 1.77 mmol) in toluene (0.40 mL) dropwise. The reaction mixture was warmed to rt for 30 min then recooled to 0°C. The intermediate aldehyde (0.5 g, 1.3 mmol) in THF (10 mL) was added dropwise and the reaction mixture was stirred at 0°C for 2 h. The solution was quenched by addition of pH 7 buffer (5 mL) and diluted with Et_2O (12 mL). The emulsion was warmed to rt and the layers were separated. The organic layer was washed with a saturated solution of NH_4Cl (10 mL) and the aqueous layers were combined and extracted with Et_2O (3 x 20ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (0% to 20% EtOAc in hexanes) to give 623 mg (70% 2 steps) of **91** a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H), 7.39-

7.37 (m, 4H), 7.21-7.18 (m, 4H), 6.85-6.83 (m, 4H), 6.98 (dd, J = 15.7, 7.6 Hz, 1H), 5.82 (dd, J = 15.7, 1.0 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 11.1 Hz, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.20 (d, J = 11.1 Hz, 1H), 3.78 (s, 6H), 3.81-3.52 (m, 4H), 2.60-2.56 (m, 1H), 1.57-1.51 (m, 2H), 1.05 (s, 9H), 1.0 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 158.9, 150.5, 131.0, 130.0, 129.2, 129.1, 121.1, 113.5, 78.4, 75.9, 71.7, 71.2, 64.1, 59.9, 55.0, 38.9, 34.1, 25.7, 18.1, 14.4, 14.1, –5.5; IR (thin film) 3055, 2956, 2933, 2908, 2857, 1705, 1243, 1097 cm^{-1}; HRMS (EI) cald for $C_{43}H_{54}O_7Si$ 710.3628, found 371.3627.

[00199] [4*R*,5*R*,7*R*]-8-(*tert*-Butyldiphenylsilanyloxy)-5,7-bis-(4-methoxybenzyloxy)-4-methyloct-2-en-1-ol. To a stirred solution of ester **91** (600 mg, 0.84 mmol) in CH_2Cl_2 (6 mL) at –40°C under argon was added slowly over 10 min via syringe DibalH in toluene (9 mL, 1M). After 30 min at –40°C, the reaction mixture was quenched by slow addition of MeOH (0.6 mL) and warmed to rt. The reaction mixture was poured into a vigorously stirred solution of saturated Rochelle salt in H_2O (8 mL) and EtOAc (12 mL) and stirred overnight. The aqueous layer was separated and extracted with EtOAc (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (20% EtOAc in hexanes) to produce 450 mg (80%) of the alcohol, a clear liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.66 (m, 4H), 7.39-7.35 (m, 6H), 7.21-7.18 (m, 4H), 6.85-6.82 (m, 4H), 5.68-5.65 (m, 2H), 4.64 (d, J = 11.1 Hz, 1H), 4.51 (d, J = 11.0 Hz, 1H), 4.46 (d, J = 11.1 Hz, 1H), 4.24 (d, J = 11.0 Hz, 1H), 4.10-4.06 (m, 2H), 3.78 (s, 6H), 3.81-3.52 (m, 4H), 2.60-2.56 (m, 1H), 1.57-1.51 (m, 2H), 1.05 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 135.6, 135.1, 133.5 (2C), 131.1, 130.3, 130.0, 127.6, 129.4, 129.6, 83.1, 75.2, 72.4, 72.2, 64.4, 63.7, 55.2, 34.7, 26.8, 19.2, 15.4; IR (thin film) 3295, 3045, 2958, 2941, 2910, 2857, 1241, 1097 cm^{-1}; HRMS (EI) cald for $C_{41}H_{52}O_6Si$ 668.3599, found 668.3596.

[00200] [2*R*,3*R*,5*R*]-8-(tert-Butyldiphenylsilanyloxy)-5,7-bis-(4-methoxybenzyloxy)-4-methyl oct-2-enal. To a solution of the alcohol (400 mg, 0.59 mmol) in CH_2Cl_2 (2 mL) was added Dess-Martin periodane (330 mg, 0.78 mmol) and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with Et_2O (10 mL) and poured into a stirring solution of saturated $Na_2S_2O_3$ (5 mL) and saturated $NaHCO_3$ (5 mL). The layers were separated and the organic layer was washed with saturated $NaHCO_3$ (3 x 5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the intermediate aldehyde which was used in the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, 7.8 Hz, 1H), 7.69-7.64 (m, 4H), 7.39-7.37 (m, 7H), 7.20-7.14 (m, 4H),

6.84-6.79 (m, 4H), 6.10 (dd, J = 7.8, 17.0 Hz, 1H), 4.64 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.1 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.18 (d, J = 11.1 Hz, 1H), 3.78 (s, 6H), 3.81-3.52 (m, 4H), 2.60-2.56 (m, 1H), 1.57-1.51 (m, 2H), 1.05 (s, 9H), 1.00 (d, J = 6.9 Hz, 3H).

[00201] [4*R*,5*R*,7*R*]-10-(*tert*-butyldiphenysilanyloxy)-7,9-bis(4-methoxybenzyloxy)-6-methyldeca-2,4-dienoicacid methyl ester. To a stirred solution of [bis-(2,2,2-trifluoroethoxy)phosphoryl]acetic acid methyl ester (210 mg, 0.65 mmol) in THF (12 mL) at –78°C under argon was added dropwise KHMDS in toluene (1.4 mL, 0.5 M). The reaction mixture was warmed to –40 °C for 1 h then cooled to –78°C and the intermediate aldehyde (400 mg, 0.59 mmol) in THF (0.5 mL) was added dropwise. After 3 h at –78 °C, the solution was warmed to 0 °C and quenched by addition of a saturated solution of NH_4Cl (5 mL) and diluted with Et_2O (5 mL). The aqueous layer was separated and extracted with diethyl ether (5 x 3 mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (10% to 30% EtOAc in hexanes), yielding 220 mg (65% 2 steps) of conjugated ester, a clear oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H), 7.39-7.37 (m, 7H), 7.20-7.16 (m, 4H), 6.85-6.79 (m, 4H), 6.64 (t, J = 11.2 Hz, 1H), 6.22 (ddd, J = 15.4, 6.8 Hz, 1H), 5.87 (d, J = 11.2 Hz, 1H), 5.04-4.99 (m, 2H), 4.64 (d, J = 11.2 Hz, 1H), 4.49 (d, J = 11.1 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.18 (d, J = 11.1 Hz, 1H), 3.78 (s, 6H), 3.81-3.52 (m, 4H), 2.60-2.56 (m, 1H), 1.57-1.51 (m, 2H), 1.05 (s, 9H), 1.00 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 147.3, 145.4, 135.6, 133.5 (2C), 130.3, 129.6, 126.7, 115.5, 113.5, 78.4, 75.9, 71.7, 71.8, 64.1, 55.0, 51.1, 39.7, 34.1, 26.8, 19.2, 14.1; IR (CH_2Cl_2) 3048, 2987, 2931, 2875, 2822, 1715, 15251, 1423, 1250, 1110 cm^{-1}; HRMS (EI) cald for 722.3642, found 722.3640 *m/z*.

[00202] [6*R*,7*S*,9*R*]-10-Hydroxy-7,9-bis-(4-methoxybenzyloxy)-6-methyldeca-2,4-dienoic acid Methyl Ester (92). To a solution of the TBDPS ether (100 mg, 0.14 mmol) in THF 1 ml) was slowly added HF-pyridine in pyridine (1.5 ml, prepared by slow addition of 0.45 ml pyridine to 0.1 ml HF-pyridine complex followed by dilution with 0.94 ml THF) at 0° C. The mixture was warmed to room temperature and stirred overnight at room temperature. The reaction mixture was slowly quenched with saturated $NaHCO_3$ (5 mL) and the aqueous layer was separated and extracted with CH_2Cl_2 (5 x 2 mL). The combined organic layers were washed with saturated $CuSO_4$ (2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (25% EtOAc in hexanes) affording 50 mg (75%) of alcohol **92**: $[\alpha]^{20}_D$ = +8.56 (*c* 0.1, $CHCl_3$); ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.53 (dd, J = 15.0, 11.4 Hz, 1H), 7.35-7.30 (m, 4H), 6.97-6.93 (m, 6H), 6.65 (dd, J = 11.3, 1.3 Hz, 1H), 6.23 (dd, J = 15.0, 6.9 Hz, 1H), 5.69 (d, J = 11.3 Hz, 1H), 4.64 (d, J = 10.9 Hz, 1H), 4.59 (d, J = 11.2 Hz, 1H), 4.44 (d, J = 11.2 Hz, 1H), 4.34 (d, J = 10.9 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 2.77-2.73 (m, 2H), 3.67-3.64 (m, 1H), 3.54 (dd, J = 3.6, 11.5 Hz, 1H), 2.95-2.89 (m, 1H), 1.90-1.81 (m, 2H), 1.19 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.0, 147.3, 145.4, 130.1, 130.3, 129.7, 126.7, 115.5, 113.6, 75.9, 78.5, 71.1, 63.9, 55.0, 51.0, 38.4, 33.7, 14.1; IR (thin film) 3315, 3055, 2986, 2858, 1710, 1513, 1423, 1247, 1105 cm^{-1}; LRMS (EI) 484, 469, 349, 425, 223, 121 *m/z*; HRMS (EI) calcd for $C_{28}H_{36}O_7$ 484.2582, found 484.2579.

[00203] (*R*,*R*)-diisopropyl tartrate (Z)-crotylboronate. An oven-dried 1L three-neck round bottom flask equipped with a magnetic stir bar and a –100 °C thermometer was charged with 206 mL of anhydrous THF and KOtBu (28.2 g, 250 mmol). This mixture was flushed with Ar and cooled to –78 °C, then cis-2-butene (23 mL, 250 mmol), condensed from a gas lecture bottle into a rubber-stoppered round bottom flask immersed in a –78 °C dry ice-acetone bath, was poured into the reaction mixture. n-BuLi (100 mL, 2.5 M in hexane) was then added dropwise via cannula over 1.5 h. After completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to –20 to –25 °C for 30 min before being recooled to –78 °C. Triisopropylborate (57.8 mL, 250 mmol) was added dropwise via cannula to the (Z)-crotylpotassium solution over 2 h. After addition, the reaction mixture was maintained at –78 °C for 30 min and then rapidly poured into a 2L separatory funnel containing 470 mL of 1 N HCl saturated with NaCl. The aqueous layer was adjusted to pH 1 by using 1 N HCl (100-150 mL), and then a solution of (R,R)-diisopropyl tartrate (52.8 g, 250 mmol) in 88 mL of Et_2O was added. The phases were separated, and the aqueous layer was extracted with additional Et_2O (4 x 120 mL). The combined extracts were dried over $MgSO_4$ for 1 h then vacuum filtered through a fritted glass funnel under Ar blanket into an oven-dried round-bottom flask. The filtrate was concentrated *in vacuo*, and pumped to constant weight at under vacuum. Anhydrous toluene (170 mL) was added to the flask make a 1M solution.

[00204] [4*S*,3*S*,2*R*]-4-Benzyl-3-(3-hydroxy-2,4-dimethylpent-4-enoyl)oxazolidin-2-one (93). Oxazolidinone 4 (10.0 g, 43.1 mmol) was treated with $MgCl_2$ (0.20 g, 2.2 mmol), $NaSbF_6$ (1.7 g, 6.5 mmol), Et_3N (6.03 mL, 86.2 mmol), methacrolein (2.67 mL, 25.9 mmol) and TMSCl (3.92 mL, 32.3 mmol) in EtOAc (50 mL) and allowed to stir under Ar at rt for 24 h. The yellow-green slurry was filtered through a plug of silica gel with Et_2O (1L). GC

analysis of the solution gave the isomeric composition of the TMS ether in a 16:1 ratio with its diastereomers. The ether was concentrated in vacuo, and MeOH (86 mL) and TFA (1 mL) was added. The reaction mixture was stirred for 30 min and concentrated to give a yellow which was purified by flash chromatography (10% acetone in hexanes) to yield 5.02 g of alcohol **93** (78% 2 steps). Data matches known literature.[32] $[\alpha]^{20}_D = +0.06$ (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H), 5.08 (s, 1H), 5.02 (s, 1H), 4.77-4.75 (m, 1H), 4.27-4.22 (m, 4H), 3.35 (dd, *J* = 13.5, 3.2 Hz, 1H), 2.83 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.75 (br s, 1H), 1.86 s (3H), 1.19 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 152.9, 145.0, 135.7, 129.3, 128.9, 127.1, 114.5, 80.1, 65.6, 55.5, 41.9, 38.4, 16.1, 14.7; IR (thin film) 3300, 3057, 2931, 2857, 1781, 1702, 1422, 1384, 1271, 1209, 1079 cm^{-1}; HRMS (EI) cald for $C_{17}H_{21}NO_4$ 303.1582, found 303.1581.

[00205] [4*R*,2*S*,3*R*]-4-Benzyl-3-[3-(*tert*-butyldimethylsilanyloxy)-2,4-dimethylpent-4-enoyl]oxazolidin-2-one. To a stirred solution of alcohol **93** (20.24 g, 66.72 mmol) in CH_2Cl_2 (170 mL) at 0 °C under argon was added 2,6-lutidine (9.3 mL, 79.85 mmol) and TBSOTf (16.1 mL, 73.4 mmol). After 3 h at 0 °C the reaction mixture was quenched with MeOH (34 mL) then concentrated to dryness. The residue was taken up in Et_2O (225 mL) and washed with a saturated solution of NH_4Cl (2 x 50 mL). The aqueous layers were combined and extracted with Et_2O (2 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the crude mixture (10% to 20% EtOAc in hexanes) gave 26.5 g (95%) of the silyl ether as a clear oil: $[\alpha]^{20}_D = +0.07$ (*c* 0.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 5.00 (s, 1H), 4.98 (s, 1H), 4.72 (dq, *J* = 7.0, 3.2 Hz, 1H), 4.51 (d, *J* = 9.6 Hz, 1H), 4.21-4.18 (m 3H), 3.49 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.64 (dd, *J* = 13.3, 10.2 Hz, 1H), 1.80 (s, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.9 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 153.1, 145.0, 135.7, 129.3, 128.9, 127.2, 114.6, 79.4, 65.8, 55.5, 41.9, 38.4, 25.8, 18.1, 16.1, 14.7, –4.7, –5.1; IR (thin film) 3047, 2938, 2854, 1779, 1702, 1429, 1380, 1271, 1210, 1082 cm^{-1}; LRMS (EI) 417, 402, 360, 290, 234, 185, 117; HRMS (EI) calcd for $C_{23}H_{35}NO_4Si$ 417.2335, found 417.2345.

[00206] [4*S*,2*S*,3*R*]-4-Benzyl-3-[3-(*tert*-butyldimethylsilanyloxy)-5-hydroxy-2,4-dimethylpentanoyl] oxazolidin-2-one (94). A stirred solution of 9-BBN in THF (29 mL, 0.5 M) was treated with the alkene (5.0 g, 11.97 mmol) in THF (29 mL). The reaction mixture was stirred at rt for 24 h, then treated sequentially with 1:1 EtOH–THF (29 mL), pH 7 buffer (29 mL) and 30% aq. H_2O_2 (14.5 mL) and stirred for 12 h at rt. The mixture was

extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with H_2O (15 mL) and saturated aqueous NaCl (15 mL) then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the mixture by flash chromatography (20% EtOAc in hexanes) gave **94** as a clear oil (3.91 g, 75%): $[\alpha]^{20}_D = +0.24$ (c 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.23 (m, 5H), 4.69-4.60 (m, 1H), 4.21 (dd, *J* = 6.8, 3.8 Hz, 1H), 4.17-4.04 (m, 3H), 3.77-3.60 (m 2H), 3.44 (dd, *J* = 13.1, 3.2 Hz, 1H), 2.60 (dd, *J* = 13.1, 10.7 Hz, 1H), 2.50 (br s, 1H), 2.02-1.85 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.9 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 153.1, 135.4, 129.3, 129.0, 127.3, 66.1, 65.4, 55.8, 43.9, 38.3, 37.0, 26.7, 26.0, 18.2, 16.4, 12.4, –4.2, –4.8; IR (thin film) 3538, 2927, 1780, 1700, 1273, 1201 cm^{-1}; HRMS (EI) cald for $C_{23}H_{37}NO_5Si$ 435.2461, found 435.2460.

[00207] (4S)-[2*R*,3*R*,4*R*]-Benzyl-3-[3,5-bis(*tert*-butyldimethylsilanyloxy)-2,4-dimethylpentanoyl] oxazolidin-2-one. To a stirred solution of alcohol **94** (2.6 g, 5.97 mmol) in CH_2Cl_2 (15 mL) at 0 °C under argon was added 2,6-lutidine (0.83 mL, 7.14 mmol) and TBSOTf (1.44 mL, 6.57 mmol). After 3 h at 0 °C the reaction mixture was quenched with MeOH (3 mL) then concentrated to dryness. The residue was taken up in Et_2O (20 mL) and washed with a saturated solution of NH_4Cl (2 x 5 mL). The aqueous layers were combined and extracted with Et_2O (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the crude mixture (10% to 20% EtOAc in hexanes) gave 3.01 g (95%) of the silyl ether as a clear oil: $[\alpha]^{20}_D = +0.24$(c 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H), 4.69-4.61 (m, 1H), 4.24 (dd, *J* = 3.7, 7.0 Hz, 1H), 4.13-4.11 (m, 3H), 3.76 (dd, *J* = 6.0, 10.3 Hz, 1H), 3.48-3.42 (m, 2H), 2.60 (dd, *J* = 10.3, 13.1 Hz, 1H), 2.01-1.87 (m, 1H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.976 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 153.1, 135.7, 129.3, 129.0, 127.3, 74.4, 66.0, 64.9, 55.7, 43.2, 39.9, 38.5, 26.1, 26.0, 18.3, 14.4, 13.5, –4.0, –4.6, –5.4 (2C); IR (thin film) 3057, 2952, 2860, 1781, 1699, 1382, 1259, 1100 cm^{-1}; LRMS (EI) 492 (M–C_4H_9), 377, 374, 199, 177, 115; HRMS (EI) calcd for $C_{25}H_{42}NO_5Si_2$ 492.3306, found 492.3301.

[00208] [2*R*,3*R*,4*R*]-3,5-bis(*tert*-Butyldimethylsilanyloxy)-2,4-dimethylpentan-1-ol (95). To a stirred solution of silyl ether (5 g, 9.09 mmol) in THF (50 mL) at 0°C were added MeOH (1.14 mL, 27.3 mmol) and $LiBH_4$ in THF (14 mL, 2M) under argon. The solution was stirred at 0 °C for 30 min and then quenched by the addition of a saturated solution of Rochelle salt in H_2O (60 mL) and stirred for 10 min at 0 °C. The mixture was poured into

CH_2Cl_2 (100 mL) and stirred vigorously until 2 layers appeared (2 h). The aqueous layer was separated extracted with of CH_2Cl_2 (40 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash chromatography (30% EtOAc in hexanes) gave 2.32 g (65%) of alcohol **95** as a colorless oil: $[\alpha]^{20}_D = +10.0$ (c 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (t, J = 5.2 Hz, 1H), 3.55-3.50 (m, 3H), 3.39 (dd, J = 10.0, 6.5 Hz, 1H), 2.98 (br s, 1H), 1.87-1.77 (m, 2H), 0.92 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.83 (s, 9H), 0.81 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H), –0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 800.2, 66.0, 65.2, 39.7, 38.8, 25.9, 25.6, 18.3, 18.0, 14.9, 14.7, –5.4, –5.3, –4.1; IR (thin film) 3330, 2930, 2858, 1471, 1250, 1023 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{44}O_3Si_2$ 376.2859, found 376.2858.

[00209] [2*R*,3*R*,4*R*]-3,5-bis-(*tert*-Butyldimethylsilanyloxy)-2,4-dimethylpentanal (96). Following the procedure for 4-(*tert*-butyldiphenylsilanyloxy)-3-(4-methoxybenzyloxy)-butyraldehyde **89**, **96** can be prepared in a similar manner.

[00210] (2*R*)-3-(*tert*-Butyldimethylsilanyloxy)-2-methylpropionic acid methyl ester. A solution of alcohol (10.0 g, 84.6 mmol), imidazole (9.2 g, 133.9 mmol), and TBSCl (19.1 g, 126.9 mmol) in DMF (150 mL) was stirred overnight at room temperature under argon. A mixture of H_2O (500 mL) and EtOAc (300 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 200 mL). The organic layers were combined and washed with H_2O (2 x 200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was purified by flash chromatography (20% EtOAc in hexanes) to yield 17.7 g (90%) of the silyl ether as a clear yellow oil: The spectral data matched that of the known compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (dd, J = 6.7, 7.0 Hz, 1H), 3.50 (dd, J = 6.7, 7.0 Hz, 1H), 3.50 (m, 3), 2.48 (sext, J = 7.0 Hz, 1H), 0.97 (d, J = 7.0 Hz, 3H), 0.71 (s, 9H), –0.1 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 65.2, 51.5, 42.5, 25.7, 18.2, 13.4, –5.5.

[00211] [2R]-3-(*tert*-Butyldimethylsilanyloxy)-2-methylpropan-1-ol. To a stirred solution of silyl ether (5.0 g, 21.5 mmol) in CH_2Cl_2 (125 mL) at –40 °C under argon was added slowly over 1.5 h via cannula DibalH in toluene (100 mL, 1M). After 30 min at –40 °C, the reaction mixture was quenched by slow addition of MeOH (15 mL) and warmed to RT. The reaction mixture was poured into a vigorously stirred solution of saturated Rochelle salt (200 mL) and EtOAc (300 mL) and stirred overnight. The aqueous layer was separated and extracted with EtOAc (3 x 50 mL), dried (MgSO4) and concentrated in vacuo. The crude mixture was purified by flash chromatography (20% EtOAc in hexanes) to produce 3.46 g

(79%) of the alcohol, a clear liquid. The spectral data matched that of the known compound: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (dd, J = 4.5, 9.8, Hz, 1H), 3.57 (m, 3H), 2.80 (br s, 1H), 1.99-1.86 (m, 1H), 0.89 (s, 9H), 0.82 (d, J = 7.0 Hz, 3H), 0.06 (d, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.8, 68.4, 37.0, 25.8, 18.1, 13.0, –5.6.

[00212] [2R]-3-(*tert*-Butyldimethylsilanyloxy)-2-methyl propionaldehyde (ent-17). DMSO (3.0 mL, 42.6 mmol) was added, dropwise, to a stirred solution of oxalyl chloride (1.5 mL, 19.9 mmol) in CH_2Cl_2 (80 mL) at –78 °C under argon. The reaction mixture was stirred for 5 min then a solution of alcohol (3.0 g, 14.7 mmol) in CH_2Cl_2 (25 mL) was added dropwise. After 1 h at –78 °C, Et_3N (10.5 mL, 74.7 mmol) was added slowly via syringe, the mixture was stirred for 5 min then warmed to room temperature. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with ice cold 0.5 M HCl (50 mL) then H_2O (30 mL) and the layers were separated. The aqueous layers were combined and extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The intermediate aldehyde **ent-17** was used in the following reaction without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (δ, 1.5 Hζ, 1H), 3.86-3.82 (m, 2H), 2.53-2.50 (m, 1H), 1.10 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

[00213] [3*S*,4*S*,5*S*]-2,4-dimethyl-1-[(*tert*-butyldimethylsilyl)oxy]-hexene-5-en-3-ol (97). A solution of (*R*,*R*)-diisopropyl tartrate (E)-crotylboronate (22.1 mmol) was added to 4 Å powdered molecular sieves (0.025 g) in toluene (1 mL) under argon and the mixture was stirred for 20 min at room temperature. The mixture was cooled to –78 °C and a solution of the aldehyde **ent-17** (3.0 g, 14.7 mmol) in toluene (8 mL) was added dropwise via syringe. The resulting mixture was maintained at –78 °C for 3 h and then treated with $NaBH_4$ (0.106 g, 2.6 mmol) in EtOH (4 mL) and warmed to 0 °C. The reaction mixture was treated with 1N NaOH (40 mL) and stirred vigorously for 30 min, followed by separation of the organic layer. The aqueous layer was extracted with CH_2Cl_2 (5 x 80 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude oil was purified by flash chromatography (5% to 25% Et_2O in hexanes) providing 2.87 g (65%) of **97**, a clear, yellow tinted oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (ddd, J = 8.8, 12.0, 15.8 Hz, 1H), 5.05 (dd, J = 1.8, 12.0 Hz, 1H), 5.04 (dd, J = 1.8, 15.8 Hz, 1H), 3.81 (s, 1H), 3.73 (dd, J = 4.2, 9.8 Hz, 1H), 3.60 (dd, J = 8.2, 9.8 Hz 1H), 3.37 (dd, J = 3.0, 4.8 Hz, 1H), 2.39-2.29 (m, 1H), 1.83-1.70 (m, 1H), 1.09 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.81 (d, J = 6.9 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9, 114.9, 80.2, 68.7, 41.2, 37.5, 25.8 [2C], 18.1, 17.7, 13.4, –5.6, –5.7.

[00214] [2*S*,3*S*,4*S*]-*tert*-Butyl-[3-(4-methoxybenzyloxy)-2,4-dimethylhex-5-enyloxy]dimethylsilane. A mixture of NaH (2.9 g, 11.6 mmol) in THF (5 mL) was cooled to 0 °C then DMF (5 mL), alcohol **97** (1.0 g, 3.87 mmol) in THF (5 mL), and PMBBr (1.8 g, 9.7 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 48 h. The resulting mixture was poured into a pH 7 phosphate buffer and diluted with ether (90 mL). The organic layer was separated and washed with pH 7 buffer (3 x 60 mL), dried over K_2CO_3, filtered and concentrated *in vacuo*. The resulting crude yellow oil was purified by flash chromatography (5% to 10% EtOAc in hexanes) providing 1.39 g (75%) of the PMB ether as a clear, yellow tinted oil: $[\alpha]^{20}_D = +0.06$ (c 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.93 (ddd, J = 15.6, 12.0, 8.3 Hz, 1H), 5.05 (d, J = 12 Hz, 1H), 5.04 (d, J = 15.6 1H), 3.89 (s, 3H), 3.29 (dd, J = 4.6, 2.9 Hz, 1H), 2.51-2.49 (m, 1H), 1.91-1.86 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 142.1, 131.2, 129.2, 114.0, 113.6, 82.8, 74.1, 65.7, 55.7, 38.4, 37.3, 25.9, 18.2, 15.6, 11.2, –5.2; IR (thin film) 3057, 2957, 2857, 1612, 1513, 1246, 1085 cm^{-1}; LRMS (EI) 323 (M – C_4H_7), 321, 271, 255, 186, 122 *m/z*.

[00215] [2*S*,3*S*,4*S*]-5-(*tert*-Butyldimethylsilanyloxy)-3-(4-methoxybenzyloxy)-2,4-dimethyl pentanal (98). Following the procedure for [2*R*,3*R*,5*R*]-6-(*tert*-Butyldiphenylsilanyloxy)-3,5-bis-(4-methoxybenzyloxy)-2-methylhexanal, **98** can be prepared in a similar manner.

[00216] (*R*,*R*)-Diisopropyl tartrate (E)-crotylboronate. An oven-dried 1L three-neck round bottom flask equipped with a magnetic stir bar and a –100 °C thermometer was charged with 206 mL of anhydrous THF and KOtBu (28.2 g, 250 mmol). This mixture was flushed with Ar and cooled to –78 °C, then trans-2-butene (23 mL, 250 mmol), condensed from a gas lecture bottle into a rubber-stoppered round bottom flask immersed in a –78 °C dry ice-acetone bath, was poured into the reaction mixture. n-BuLi (100 mL, 2.5 M in hexane) was then added dropwise via cannula over 1.5 h. After completion of the addition, the cooling bath was removed and the reaction mixture was allowed to warm to an internal temperature of –50 °C for 15 min then immediately recooled to –78 °C. Triisopropylborate (57.8 mL, 250 mmol) was added drop-wise via cannula to the (E)-crotylpotassium solution over 2 h. After addition, the reaction mixture was maintained at –78 °C for 30 min and then rapidly poured into a 2L separatory funnel containing 470 mL of 1 N HCl saturated with NaCl. The aqueous layer was adjusted to pH 1 by using 1 N HCl (100-150 mL), and then a solution of (R,R)-diisopropyl tartrate (52.8 g, 250 mmol) in 88 mL of Et_2O was added. The

phases were separated, and the aqueous layer was extracted with additional Et_2O (4 x 120 mL). The combined extracts were dried over $MgSO_4$ for 1 h then vacuum filteredthrough a fritted glass funnel under Ar blanket into an oven-dried round-bottom flask. The filtrate was concentrated *in vacuo*, and pumped to constant weight at under vacuum. Anhydrous toluene (170 mL) was added to the flask make a 1M solution.

[00217] Biology

[00218] General. Tubulin without microtubule-associated proteins was prepared from fresh bovine brains.[32] The normoisotopic and tritiated forms of paclitaxel and normoisotopic docetaxel were provided by the Drug Synthesis and Chemistry Branch, National Cancer Institute. (+)-Discodermolide was from Novartis Pharmaceutical Corporation. Ca^{2+}- and Mg^{2+}-free RPMI-1640 culture medium were from GIBCO/BRL-Life Technologies. Fetal bovine serum (FBS) was from Hyclone. Cell lines were obtained from American Type Culture Collection (Manassas, VA).

[00219] Tubulin Polymerization.[32] Tubulin assembly was followed in a Beckman-Coulter 7400 spectrophotometer, equipped with an electronic Peltier temperature controller, reading absorbance (turbidity) at 350 nm. Reaction mixtures (0.25 mL final volume) contained tubulin (final concentration 10 μM; 1 mg/mL), monosodium glutamate (0.8 M from a stock solution adjusted to pH 6.6 with HCl), DMSO (final volume 4% *v/v*), and differing concentrations of test agent where indicated. Reaction mixtures without test agent were cooled to 0 °C and added to cuvettes held at 0.25-0.5 °C in the spectrophotometer. Test agent in DMSO was then rapidly mixed in the reaction mixture. Each run contained one positive control (paclitaxel, 10 μM final concentration) and one negative control (DMSO only). Baselines were established at 0.25-2.5 °C and temperature was rapidly raised to 30 °C (in approximately 1 min) and held there for 20 min. The temperature was then rapidly lowered back to 0.25-2.5 °C.

[00220] Cell Growth Inhibition[34] Cells were plated (500-2000 cells/well depending on the cell line) in 96-well microplates, allowed to attach and grow for 48 h, then treated with vehicle (4% DMSO, a concentration that allowed doubling times of 24 h or less) or test agent (50, 10, 2, 0.4 and 0.08 μM for the new agents; 0.001, 0.005, 0.010, 0.020 and 0.100 μM for paclitaxel and discodermolide) for the given times. One plate consisted of cells from each line used for a time zero cell number determination. The other plates in a given determination contained eight wells of control cells, eight wells of medium and each agent concentration tested in quadruplicate. Cell numbers were obtained spectrophotometrically (absorbance at 490 nm minus that at 630 nm) in a Dynamax plate reader after treatment with

3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) using phenazine methanesulfonate as the electron acceptor. After initial screening with the above 5-fold dilutions, fifty percent growth inhibitory concentration (GI_{50}) values were determined for each agent by repeating the screen using 2-fold dilutions (five concentrations) centered on the initial estimated GI_{50} concentration, again in quadruplicate.

[00221] Paclitaxel binding site inhibition assay. [34] A stock solution of [^{3}H]paclitaxel (26.8 μM, 16.2 Ci/mmol), obtained from the NCI, was prepared in 37% (*v/v*) DMSO. The test agents were prepared in 25% (*v/v*) DMSO-0.75 M monosodium glutamate (prepared from a 2M stock solution adjusted to pH 6.6 with HCl). The radiolabeled paclitaxel and test agents, as indicated in terms of final concentrations, were mixed in equal volumes and warmed to 37 °C. A reaction mixture (50 μL) containing 0.75 M monosodium glutamate, 4.0 μM tubulin, and 40 μM ddGTP (a non-hydrolyzable analog of GTP) was prepared and incubated at 37 °C for 30 min to preform microtubules. An equivalent volume of drug mixture with [^{3}H]paclitaxel was added to preformed polymer and incubated for 30 min at 37 °C. Bound [^{3}H]paclitaxel was separated from free drug by centrifugation of the reaction mixtures at 14000 rpm for 20 min at room temperature. Non-specific binding was determined by addition of a 12-fold excess of docetaxel. Radioactive counts from the supernatant (50 μL) were determined by scintillation spectrometry. Bound [^{3}H]paclitaxel was calculated from the following: total paclitaxel added to each reaction mixture minus the paclitaxel present in the supernatant (free drug). The % bound values were normalized to the control values with no inhibitor added.

[00222] The foregoing description and accompanying drawings set forth the preferred embodiments of the invention at the present time. Various modifications, additions and alternative designs will, of course, become apparent to those skilled in the art in light of the foregoing teachings without departing from the scope of the invention. The scope of the invention is indicated by the following claims rather than by the foregoing description. All changes and variations that fall within the meaning and range of equivalency of the claims are to be embraced within their scope.